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ELECTRON MICROSCOPE STUDIES OF THE STRIA VASCULARIS AND SPIRAL LIGAMENT AFTER FERRITIN INJECTION

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Abstract Electron microscope studies of the transport and diffusion of macromolecules across the lateral wall of the cochlear duct were made after endolymphatic or perilymphatic injection of ferritin. After endolymphatic injection, the cells of the attachment zone of Reissner's membrane, the marginal cells of the stria vascularis, and cells of the spiral prominence and external sulcus absorbed the tracer but do not transport it across their cytoplasm. No ferritin was ever found in the spiral ligament After ferritin injection into the perilymph the tracer was found in the spiral ligament and in the endothelial cells and lumen of the spiral ligament capillaries. Also it was found in cells of the attachment zone of Reissner's membrane, spiral prominence and external sulcus. In the stria vascularis ferritin was found only in the apical cytoplasm of the marginal cells. This was explained by transport from perilymph to endolymph across Reissner's membrane. The functional significance of these findings were discussed.

Electron microscope studies of a tracer's transport by structures of the cochlear duct may provide useful information about the mechanisms underlying transport of substances in the inner ear Yamamoto & Nakai (1964) introduced iron dextran into the perilymph, endolymph and the venous system the following conclusions emerged from this study *a*) there is a uni-directional transport system from endolymphatic space to capillaries across the spiral prominence and external sulcus cells *b*) there is a similar transport system from perilymphatic space to capillaries *c*) the endothelial cells of the capillaries offer a barrier to the transport of iron dextran from blood to tissue. Ilberg (1968) studied the transport of thorium dioxide by the stria vascularis and spiral ligament after injecting the tracer either into the endolymph or the perilymph. He found that the spiral ligament, and both the scala vestibuli and tympani constituted a single perilymph-filled space in the sense that perilymph could pass freely from one scala to the other through the spiral ligament he found also that the capillaries of the spiral ligament interposed in this pathway did not transport thorium dioxide from perilymph to the blood stream The observations also showed that the cells of the stria vascularis and spiral ligament lining the scala media served as a barrier preventing transport of macromolecules from endolymph to perilymph, however the marginal cells of the stria readily absorbed the tracer but there was no evidence of tracer transport across the cells.

Duvall et al. (1971) injected the enzyme horseradish peroxidase intravenously as a tracer and observed that it crossed the endothelial cells of the capillaries at the level of the stria vascularis. The blood vessels of the spiral ligament and spiral prominence were impermeable to the tracer The enzyme that crossed the endothelial cells from the blood to the strial tissue was absorbed only by the intermediate cells of the stria, the marginal and basal cells did not absorb the tracer

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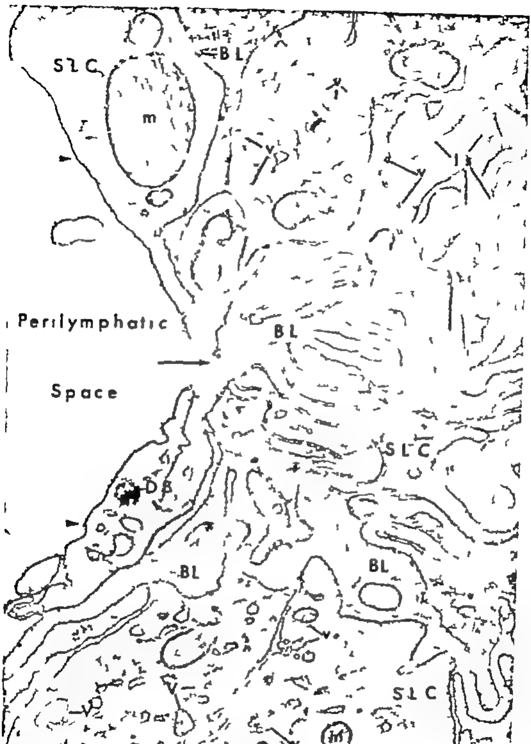


Fig. 1. Portion of the spiral ligament in the scala vestibuli of the cat (i.e. above the junction with Reissner's membrane) 1 hour after injection of ferritin in the perilymph. The tracer is seen in small clusters (arrow heads) directly apposed to the free surface of the spiral ligament cells (*SLC*); these cells have accumulated ferritin in vesicles ( ), vacuoles (*V*) and dense bodies (*DB*). Spiral ligament cells lining the perilymphatic space are frequently separated by irregular spaces (*arrow*) where the perilymph makes contact with the basal lamina (*BL*). Ferritin molecules have accumulated in the basal lamina and intercellular spaces (*Is*). *m* Mitochondria. × 28 000.

Fig. 2. A section of the basal zone of the stria vascularis connecting with the spiral ligament, 1 hour after injection of ferritin in the perilymph. Ferritin molecules (*f*) are seen both free and between fibrils found in the intercellular spaces between spiral ligament cells (*SLC*). Molecules of the tracer are seen in vesicles ( ) and in a vesicular invagination (*arrow*) of spiral ligament cells. No ferritin molecules were observed in marginal (*MC*) or basal cells (*BC*) of the stria vascularis. *BL*, Basal lamina. × 27 590.

Observations of the transport of tracers of the cochlear-duct structures are limited in number and to a certain extent, controversial thus the process requires further investigation In the study reported here ferritin was used as a tracer and its transport after injection in perilymph or endolymph was studied with electron microscopy

MATERIAL AND METHODS

Twenty-nine healthy adult cats were used in the experiment Each animal was anesthetized with intraperitoneal pentobarbital sodium (30 0 mg per kilogram of body weight) the head was fixed rigidly and a tracheotomy was performed The middle ear was opened, the round and oval windows exposed and ferritin was then injected either into the perilymph or the endolymph The technique for injection of ferritin into the endolymph and perilymph was identical to that described previously (Hinojosa, 1971). The amount of ferritin injected into the endolymph was estimated to be between 0 08 and 0 40 μl The amount of ferritin solution injected into the perilymph varied from 0 4 to 2.0 cc.

The cochlea was fixed with 1 or 2.5% solu- of osmium tetroxide in *s*-collidine buffer 7 4 using the intravital perfusion technique described previously (Hinojosa, 1971) Following fixation each animal was decapitated and the cochlea separated from the temporal bone Part of the lateral wall of the otic capsule was then removed and the cochlea immersed in osmium tetroxide fixative for 3 1/2 hours The material was then transferred to 70% ethanol and, while in this solution, the cochlea was trimmed under a dissecting microscope into smaller pieces. The specimens were dehydrated in a graded series of ethanol solutions, embedded in Epon 812 (Luft, 1961) and sectioned in an LKB ultrotome III. Sections were stained with lead tartrate (Millonig, 1961) or lead citrate (Reynolds, 1963) and examined in a Philips EM 300 electron microscope operated at 40 kv

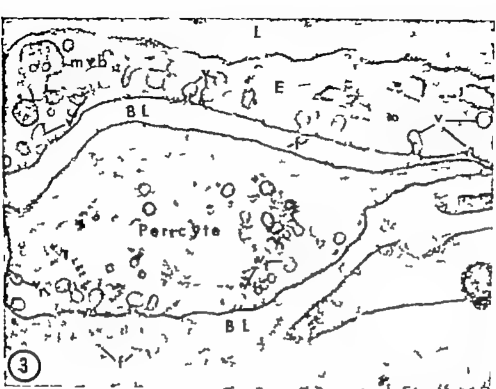
OBSERVATIONS

Perilymphatic injection

Electron microscope observations were made of animals killed between 1 and 2 hours following perilymphatic injection of ferritin The tracer appeared in different structures of the cochlear duct as follows

1 *Spiral ligament* Ferritin molecules were found in the cells, in the blood vessels, and the intercellular spaces of all areas of the spiral ligament (Figs. 1 2) Type II spiral ligament cells (Takahashi & Kimura, 1970) absorbed ferritin in moderate quantity these cells are found near the surfaces of both the scala vestibuli and the scala tympani, behind the epithelium of the spiral prominence and behind the external sulcus cells. The tracer accumulated in these cells in numerous small pinocytosis vesicles and vacuoles distributed throughout the cytoplasm (Fig. 1) The spiral ligament cells lining the scala vestibuli are frequently separated from each other leaving spaces where the basal lamina (basement mem-

Fig 3 A portion of the wall of a capillary from the spiral ligament hours after injection of ferritin in the perilymph The endothelial cell (*E*) shows micropinocytosis vesicles ( ) and a multivesicular body (*mvb*) containing ferritin Molecules of the tracer (*f*) are accumulated in the basal lamina (*BL*) which surrounds the pericyte *This cell shows micropinocytosis* vesicles (v_1) containing ferritin Notice the concentration of these vesicles at the side of the pericyte opposite the endothelial cell *L*, Capillary lumen. 46 170
Fig. 4 A higher magnification of a portion of the wall of another capillary from the spiral ligament 2 hours after injection of ferritin in the perilymph Ferritin molecules are visible in micropinocytosis vesicles ( ), at the base of the endothelial cell (*E*), in vesicles located in the cytoplasm (v_1) and in a vesicle apparently fused with the plasmalemma of the luminal surface of the cell (v_2). Ferritin (*f*) is also *found* accumulated in the basal lamina (*BL*). The pericyte (*P*) shows a few labeled vesicles (*v*). *Inset:* The inset shows a portion of an endothelial cell with a micropinocytosis vesicle (*v*) opened on the capillary lumen and a free ferritin molecule (*f*). *L*, Capillary lumen, *m*, Mitochondria 53 350. Inset, × 86 184.


L
myb
E
BL
v
f
Pericyte
BL
3


L
m
E
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P
f
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4

brane) is in direct contact with the peri lymphatic fluid (Fig. 1) similar observations have been made on the cells lining the scala tympani. Numerous ferritin molecules pene trated the spiral ligament through these spaces and were found accumulated in the basal lamina and the intercellular spaces between spiral ligament cells (Figs 1 2)

Type I cells absorbed ferritin in small quan tities (Fig. 2) these cells are found in the deeper part of the spiral ligament and adjacent to the stria vascularis. The tracer absorbed by pinocytosis vesicles, accumulated in small vacuoles in their cytoplasm

The blood capillaries in the spiral ligament have a continuous endothelial lining and a distinct basal lamina they are partially sur rounded by pericytes or pericapillary cells. Ferritin molecules were seen in all of these elements, i.e., pericytes, basal lamina and endothelial cells The pericytes showed a few micropinocytosis or plasmalemmal vesicles containing ferritin, accumulated close to the cell surface opposite the endothelial aspect of the pericyte (Figs. 3 4) The accumulation of ferritin in the pericytes was limited to a few molecules in small vacuoles. Ferritin was in the endothelial cells but not in the rcellular spaces between them The tracer was found in plasmalemmal vesicles located either in the tissue aspect, deeper in the cytoplasm or in the blood aspect of the endothelial cells (Figs. 3, 4) No tracer was found free in the cytoplasm of any of these cells. The tracer labeling was greater in the vesicles on the tissue aspect than in those of the blood aspect. A few labeled vesicles were seen opened on the cell surface of the blood aspect and few fer tin molecules were still seen in their lum (Fig 4 inset) A few tracer molecules we found accumulated in small vacuoles and mu tivesicular bodies of the endothelial ce (Fig 3).

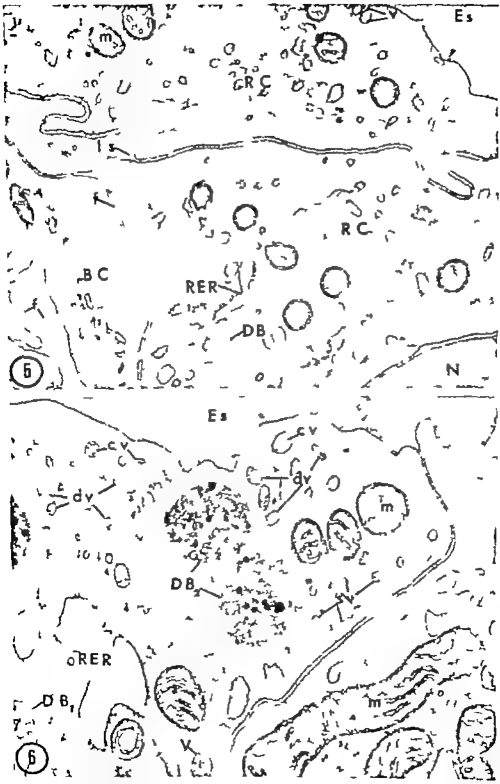
2 *Attachment zone of Reissner s membran* Ferritin molecules were found within the ce of the zone of attachment of Reissne membrane to the spiral ligament and in t intercellular spaces between them up to t zonula occludens but not within the zonula it self (Fig 5) A few pinocytosis vesicles containing ferritin can be seen close to the basal and apical plasmalemma of these cells. The tracer was accumulated in small dense bodies within the cytoplasm of the cell and also was found attached to small areas of the filamentous coating of the free surface of the cells (Fig. 5)

3 *Stria vascularis* The basal cells, inter mediate cells and the lower four fifths of the marginal cells (infranuclear area) and the intercellular spaces were free of ferritin molecules (Fig. 2) However ferritin was found in the supranuclear area of the marginal cells accumulated in coated dense and small vesicles, vacuoles and dense bodies (Fig 6). The tracer was also found apparently attached to localized areas of the filamentous coating of the free surface of the marginal cells.

4 *Spiral prominence and external sulcus* Ferritin molecules were seen in a few organ elles within the cells as well as in the intercel lular spaces. A few labeled pinocytosis vesicle and vacuoles were found concentrated near th basal and/or the apical cytoplasm of thes

Fig 5 Cells of the zone of insertion of Reissner's membrane (*RC*) to the spiral ligament, 2 hours after perilymphatic injection of ferritin. Molecules of tracer are seen attached to areas of filamentous coating of the free surface of the cells (arrow head), in vesicles (r) and in a dense body (*DB*) Ferritin (*f*) is also found free in the intercellular spaces (*Is*) between Reissner s cells (*RC*) and in the ntercellular substance between basal cells (*BC*) and cell of the spiral ligament. *Es*, Endolymphatic space *m* Mitochondria, *RER* Rough endoplasmic reticulum N Nucleus. ×34 790.

Fig 6 Two adjacent marginal cells of the stri vascularis 2 hours after injection of ferritin in the perilymph. Molecules of tracer are seen attached to extensive areas of external filamentous coating of the luminal surface of the cells, as well as in coated vesicles (*cv*), dense vesicles (*dv*), small vesicles (*v*) a vacuole (*V*), and a dense body (*DB*₁) located in the apical cytoplasm. Other dense bodies (*DB*₂) contain no ferritin molecules. *Es*, Endolymphatic space; *RER* Rough endoplasmic reticulum, *m* Mitochondria 41 496.


Es
m
GRC
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BC
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DB
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Es
cv
dv
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structures has been found to be a barrier against diffusion of macromolecules similar findings have been made in other epithelia by several authors (Becker et al., 1967 Hampton & Rosario 1967 Ilberg 1968 Hinojosa, 1971)

These findings indicate that the structures forming the lateral limiting wall of the scala media represent a barrier against transport and diffusion of macromolecules between endolymph and perilymph Similar findings were reported by Ilberg (1968) in the guinea pig after injection of thorium dioxide On the other hand, Yamamoto & Nakai (1964) found that following the injection of iron dextran in the scala media of the guinea pig cochlea the tracer either diffused between intercellular spaces or was transported across the cells of the spiral prominence and external sulcus they also found the tracer in the spiral ligament and in the endothelial cells of the capillaries. The present experiments do not confirm the findings of Yamamoto and Nakai.

Fig. 13 summarizes the results of the injection of ferritin into the perilymphatic space The long arrows crossing Reissner s membrane (*rm*) and the endothelial cells of the capillaries (c) represent active transport across the cells of these structures. The arrows in the wide intercellular spaces of scala vestibuli and scala tympani represent the diffusion of ferritin from the perilymph towards the spiral ligament. Ferritin injected into the perilymphatic space infiltrated the spiral ligament through wide intercellular spaces between the lining cells of scala vestibuli and scala tympani The wide discontinuities between the lining cells were described in the rat by Iurato (1967) in the guinea pig by Ilberg (1968) and in the monkey by Takahashi & Kimura (1970) Spoendlin & Balogh (1963) found the discontinuities only in the tympanic portion of the spiral ligament of the cat cochlea. In our material the discontinuities between lining cells were observed in the spiral ligament of both scalae The tracer accumulated in the basal lamina and the intercellular spaces and was taken up by the cells of the spiral ligament including the cells lining both scalae Ferritin accumulated in moderate quantity in some of these cell's organelles (vesicles, vacuoles, dense bodies)

Another important observation was the transport of ferritin across the endothelial cells of the capillaries of the spiral ligament. Apparently the endothelial cells of all capillaries of the spiral ligament regardless of their location adsorb and transport ferritin towards the blood The tracer is transported in the endothelial cells by plasmalemmal vesicles from tissue aspect towards blood aspect

Transport of macromolecules in the opposite direction, that is, from blood aspect of spiral ligament capillaries to tissue aspect has not been demonstrated When either iron dextran (Yamamoto & Nakai, 1964) or horseradish peroxidase (Duvall et al., 1971) was injected intravenously no tracer was ever transported across the endothelial cells of the spiral ligament capillaries although absorption by these cells was demonstrated In other tissues however transport of ferritin by plasmalemmal vesicles from blood aspect to tissue aspect was described by Bruns & Palade (1968) in muscle capillaries, and by Florey (1967) in the endothelium of the liver adrenal, spleen, heart, lung, pancreas and small intestine capi-

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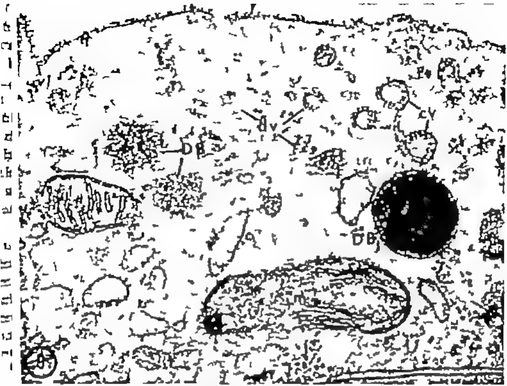
Fig 9 Apical cytoplasm of a marginal cell of the stria vascularis one hour after injection of ferritin in the endolymph Numerous ferritin molecules are seen apparently attached to the external filamentous coating of the luminal surface (arrow head), as well as in the coating of a vesicular invagination (*vi*). Coated vesicles (*cv*), tubular structures (*t*), dense vesicles (*dv*) and dense bodies (*DB*) all containing ferritin, are seen accumulated close to the surface of the cell. One dense body (*DB*) shows numerous dense particles but apparently has no ferritin molecules. *m* Mitochondria. ×49 250.

Fig 10 Portion of the apical cytoplasm of a marginal cell 2 hours after injection of the ferritin in the endolymph. The tracer is found in dense vesicles (*dv*), a vacuole (*V*) and dense bodies (*DB₁*). Other dense bodies (*DB*) show numerous dense particles but apparently have no ferritin molecules. *RER* Rough endoplasmic reticulum. ×51 300



dv
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DB
DB
9

RER
dv
DB
DB
dv
V
DB
10

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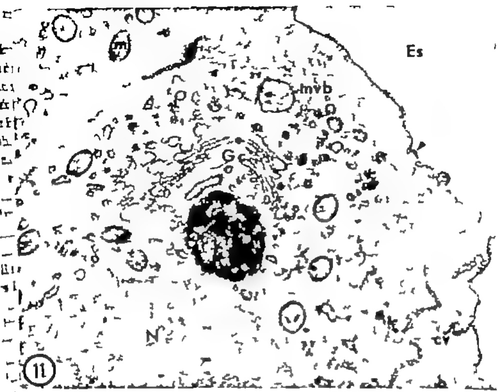

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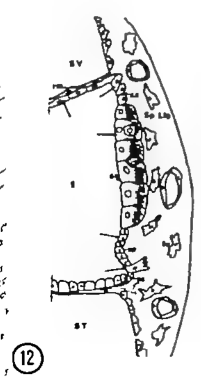

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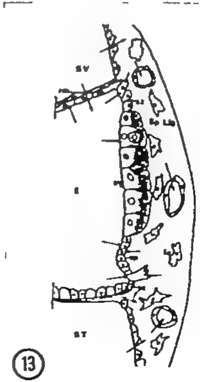

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distribution of the tracer within the cells. The observations clearly showed that the ferritin containing organelles are accumulated near both the basal plasmalemma (absorbed from the spiral ligament) and the plasmalemma of the free surface (absorbed from endolymph) and that no ferritin was ever observed in the mid-portion of the cell (Figs 5 7 8) This finding strongly suggests there is no transport of tracer through the cytoplasm in either direction

ZUSAMMENFASSUNG

Untersuchungen über die Beförderung und Diffusion von Makromolekülen über die seitliche Wand des Ohrschneckenganges wurden nach endolymphatischen bzw perilymphatischen Injektionen von Ferritin auf dem Elektronenmikroskop gemacht. Nach endolymphatischer Injektion nahmen die Zellen der Anheftungszone von Reissners Membran, die randständigen Zellen der Stria vascularis, und Zellen der Prominentia spiralis und des Sulcus externus das Spurenmaterial auf, leiteten es jedoch nicht über ihr Cytoplasma. Es wurde niemals Ferritin im Spiralligament festgestellt. Nach der Ferritin Injektion in die Perilymphe konnte Spurenmaterial im Spiralligament, in den Endothelzellen und im Lumen der Spiralligamentkapillaren festgestellt werden. Es war ebenfalls in der Anheftungszone von Reissners Membran, der Prominentia spiralis und dem Sulcus externus vorhanden. In der Stria vascularis wurde nur im apikalen Cytoplasma der randständigen Zellen Ferritin festgestellt. Diese Feststellung wurde durch die Beförderung von der Perilymphe zur Endolymphe über Reissners Membran autert Die funktionelle Bedeutsamkeit dieser Ergeb-
-- wurden erörtert.

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HUMAN ACOUSTIC NERVE ACTION POTENTIAL RECORDINGS FROM THE TYMPANIC MEMBRANE WITHOUT ANESTHESIA

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Abstract. A non-surgical method for recording human acoustic nerve action potentials is described. Data obtained from 18 subjects with normal hearing are presented, and a relationship between stimulus intensity and latency of the N component of the acoustic nerve response is given. Possible application of this relationship as a reference in diagnosing hearing disorders is discussed.

Interest in objectifying audiologic evaluation has led to efforts to develop techniques for recording cochlear electrical signals from humans. Early attempts to record this activity concentrated on obtaining a.c. cochlear potentials (CPs) (Fromm et al., 1935 Lempert et al., 1947 Ruben et al., 1961) The majority of recent studies have used averaging techniques to recover acoustic nerve action potentials (APs) elicited by transient stimuli since these potentials reflect both hair cell function and activity in the afferent fibers of the acoustic nerve

Sohmer & Feinmesser (1967) reported human AP data recorded from an electrode placed on the ear lobe They chose this site as optimal from a standpoint of convenience and reproducibility after investigating electrode placements in the round window niche and on the tympanic membrane The magnitude of the potentials obtained from this location, however was less than 0.5 μv to a 115 dB SPL stimulus. Coats & Dickey (1970), and Yoshie et al. (1967) reported AP data obtained by placing a small needle in the posterior wall of the canal. Both groups demonstrated potentials greater than 1 μv for recordings at stimulus levels well below the intensities used by Sohmer & Feinmesser (1967) Aran & LeBert (1968) have employed a technique for recording APs that places an active electrode on the promontory by tympanic membrane puncture Their technique has also yielded response amplitudes of several μv

Placement of an electrode on the promontory or in the wall of the meatus would seem to offer two major advantages:

1 AP voltages in the order of one to several μ are obtained. This improves the signal-to-noise ratio and reduces the effects of movement artifacts, etc.

2. APs can be obtained for stimulus intensities below the maximum output [illegible] speakers, thereby permitting [illegible] latency or response amplitude [illegible] a function of stimulus intensity

These techniques, however [illegible] stration of an anesthetic [illegible] tion of the tympanic membrane and [illegible] of the external meatus. [illegible]

This research was supported in part by funds obtained through National Institutes of Health General Research Support Grant FR5376, USPHS Grant No. 07533 and a grant from the Deafness Research Foundation to the Louisiana State University School of Medicine. Necessary laboratory facilities were provided through a grant from the Kresge Foundation

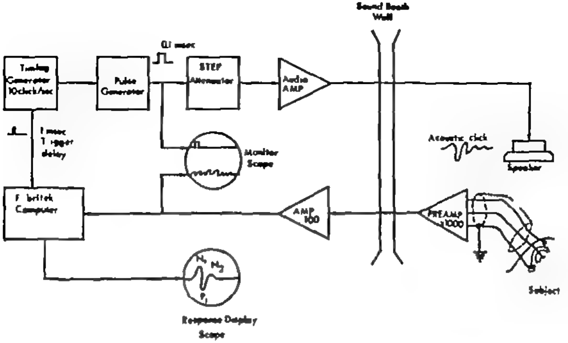

Fig 1 Block diagram of stimulus and response recording system.

eral application of the techniques and is in contrast to the simpler procedure of Sohmer & Feinmesser which requires only attachment of external disk electrodes.

We wish to report a new technique for recording APs from humans which incorporates most of the advantages of previously discussed procedures without the concomitant limitations We undertook this development with the following objectives in mind

1 To provide a method for recording APs which yielded results comparable to meatal wall or promontory recordings but was truly "non-surgical."

2 To generate an input–output function with statistically meaningful limits in order to establish a base line for the future investigation of these functions in known hearing disorders.

METHOD

We chose the posterior inferior quadrant of the tympanic membrane as our recording site. By placing an electrode as near as possible to the juncture of the annulus and the meatal wall, we minimized the conduction pathw between the round window and the electrode

The active electrode probe was construct from 4 cm of fine silver wire (0.5 mm D sheathed with teflon tubing. A 1 0 mm silve silver chloride ball electrode (Invivo Metr Systems) was soldered to the tip of the prob The active electrode and both ground an reference electrodes (silver/silver chlori disks, Invivo Metric Systems, Type SE-D) we kept equilibrated by immersion in norm saline Prior to each recording session, a sma pledget of cotton was wrapped about the ba tip of the active electrode probe and saturat with saline.

Potentials recorded with our electrode ar rangement were amplified with a Tektron 122 preamplifier located near the subject. Sig nals were further amplified by a 40 dB ampl fier for summation and display via a Fabrite 1062 computer Timing and stimulus puls were generated by combination of a Systron Donner 100A pulse generator and 410 func tion generator Stimulus pulses of 0 1 mse duration were delivered at a rate of 10/sec.

second delayed pulse was used to trigger the summating computer

Stimulus pulses were taken from the function generator and fed to a Dynaco audio amplifier through a Hewlett Packard 350D attenuator. The output of the amplifier was used to drive a TDH-49/10Z headphone mounted on a standard laboratory ring stand. A block diagram of both the stimulus generation and response recording systems is shown in Fig. 1.

Procedure

We carefully calibrated our stimulus system in order to specify the intensity and spectral characteristics of the click used in these studies. A Brüel & Kjaer 4133 condenser microphone was placed at zero incidence to the diaphragm of the speaker at a distance of 12 inches. Examination of the output of the microphone showed that the first peak of the click was compressional. This polarity was maintained throughout our study.

Peak SPL calibrations were obtained by matching on an oscilloscope, peak voltage of the transduced click to the peak voltage of a 4 kHz sine wave signal produced by the driver. Peak sound pressure levels of the 4 kHz test signal were read in dB re 0.0002 dyne/cm^2 using a Brüel & Kjaer 2604 microphone amplifier. This measurement was then taken as the peak sound pressure level of our stimulus (Yoshie & Ohashi, 1969).

The overall linear dynamic range of our complete stimulus system was determined in two ways: first, the attenuator characteristic was checked using a 4 kHz signal. Output of the TDH-49/10Z driver was measured in dB SPL during these tests. Second, click spectra were obtained for all test settings using the previously-mentioned Brüel & Kjaer equipment and a Tektronix 3L5 spectrum analyzer.[1] Distortion of the click was noted to occur at levels above 90 dB peak SPL. Attenuation characteristics below this level were within 0.5 dB of nominal. Since distortion products were a small percentage of the total energy output to a level of approximately 110 dB peak SPL, attenuator correction curves were drawn thereby permitting testing above 90 dB peak SPL.

Subjects were tested in a sound room while lying comfortably on a couch or examining table. The ear of the subject was viewed by means of a head lamp and speculum. Excess cerumen was removed, and the ear was flushed with a small amount of sterile saline. No preparation beyond this simple procedure was found to be necessary.

The active electrode probe was placed against the tympanic membrane and held relatively stationary by means of a small strip of paper tape affixed to the probe lead wire. A reference disk was attached to the prominence of the mastoid using paper tape and standard EKG electrode paste. Likewise, a ground disk was attached to the earlobe. Both disk attachment sites were cleaned with a mild detergent and acetone prior to placing the electrodes in order to minimize skin resistance. During testing, the TDH-49/10Z driver was maintained at 12 inches from the canal opening of the ear. A subject positioned for testing is shown in Fig. 2.

Subjects

A total of 18 subjects between the ages of 19 and 40 years were tested. All had pure tone thresholds better than 20 dB ISO for frequencies between 125 and 10 kHz for the ear or ears tested. Pre-testing audiometric evaluation was accomplished by continuous tone Békésy tracings.

Test protocol

After placement of the electrodes and positioning the driver the subject was allowed a few minutes to acclimate to the testing situation. A threshold for the click stimulus was then determined using an ascending technique. Five experimental runs with stimulus levels

[1] The spectrum of this stimulus covered a range of 100 to 7 kHz, with a dominant energy peak at 4.2 kHz.

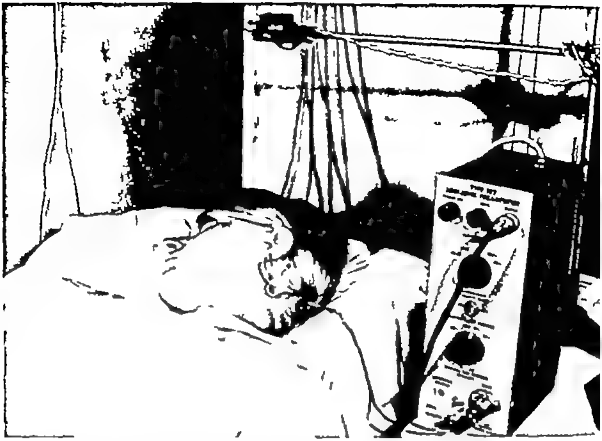

Fig 2 Normal subject positioned for recording acoustic nerve action potentials.

between 54 and 102 dB peak SPL were made, g 40 dB above the subject's threshold. Two silent runs were also included in the protocol. The first silent run preceded any of the experimental runs the second followed the completion of testing All experimental runs were made in an ascending order in 10 dB steps. A retest run was made at 60 dB sensation level immediately following the last experimental run to confirm the repeatability of the AP data.

Each run of the procedure consisted of 1 024 stimulus presentations with each response summed in 256 memory locations of the Fabritek The sampling rate of the computer was set to 50 μsec per point Low pass filtering was employed to restrict the bandpass of the response recording system to 1 kHz. This limitation helped reduce noise without greatly distorting the N_1 component of the response which had a rise time of approximately 0· msec

Six of the 18 subjects had both right and le ears tested in the context of the general protocol outlined above, but with fixed stimuli levels of 57.5 67.5 77.5 87.5 and 96 dB peak SPL. Retest runs were made in each of these subjects at 77.5 dB peak SPL. Data obtained in this sub-experiment were used to statistically assess measured differences between ears and test conditions (see Results)

Data analysis

Latency of the first negative peak of the AP was measured for each run in which an unambiguous response could be seen Latency was determined from the calculated time of arrival at the entrance to the external meatus No attempt was made to correct these times for the length of the external canal, since th

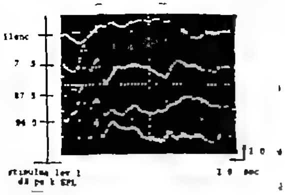

Fig 3 Acoustic nerve action potentials recorded from a normal subject.

could not be determined with any great accuracy and the additional conduction time approached the temporal resolution of the Fabritek (50 μsec) Latencies were determined by measuring from Polaroid photographs of the computer readout on an oscilloscope (Fig. 3) Measurements were made by two of the investigators working independently Differences between measurements greater than 100 μsec were resolved by a third measurement, where differences were less than 100 μsec, the lesser of the two measures was accepted. A 1 msec delay between the onset of the stimulus pulse and the start of response processing with the Fabritek was introduced to eliminate stimulus artifacts which occasionally occurred at the higher stimulus intensities. This delay was considered in determining all response latencies

RESULTS

We were able to record clearly defined acoustic nerve action potentials in *all* subjects at 60 dB sensation level [1] In 15 of the 28 ears tested, AP data were recorded at or below 90 dB sensation level.

The data of the 6 subjects tested with fixed SPL s for right and left ears are listed in Table I. An analysis of variance for these data shows that differences between right and left ears are non-significant differences in latencies as a function of stimulus level are significant at $P < 01$ F (3 40) = 13.34 Pooling the latency data across ears and examining the differences in rank ordered means using Tukey s Q as adapted by Snedecor (1966) demonstrates a significant difference ($P < .05$) between all paired means except the 77.5 dB peak SPL run and the retest run (also at 77.5 dB peak SPL) and between experimental runs at 96.0 and 87.5 peak SPL.

Fig 4 is a plot of latency versus click level representing all data from the 18 normal subjects tested, including the 6 subjects whose test results are discussed above. These data represent 101 test runs for which measurable N_1 latencies could be obtained. A total of 28 ears are represented—14 right and 14 left.

In order to provide a descriptive relationship between stimulus level and N_1 latency a curve has been fitted to these data using regression techniques (U.S Forest Service

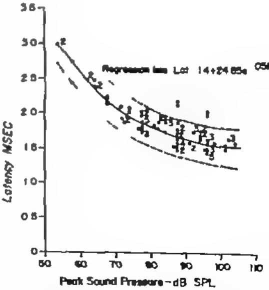

Fig 4 Scatter plot of N_1 latency versus stimulus intensity for 14 left ears and 14 right ears. A total of 101 experimental runs are included. Heavy black line represents the plot of the regression line broken curves represent 90% limits assuming a normal distribution of the residual about the regression line.

The average behavioral stimulus threshold determined for our subjects occurred at a click level of 17 dB peak SPL.

Table I *Latency of N_1 component of the acoustic nerve action potential recorded from left and right ears of 6 subjects*

	Stimulus, Level, dB Peak SPL							
	77.5		87.5		96.0		77.5 (Retest)	
Subject	Left	Right	Left	Right	Left	Right	Left	Right
N B	2.30[a]	2.00	2.15	1.65	2.00	1.60	2.30	2.00
E. K.	2.00	1.95	1.60	1.80	1.45	1.60	1.90	2.15
J P	1.90	1.85	1.75	1.65	1.50	1.50	1.85	1.85
B. V	1.90	2.05	1.60	1.90	1.55	1.65	1.85	2.05
V M	1.75	1.75	1.60	1.50	1.45	1.45	1.75	1.75
R. M.	1.75	1.90	1.60	1.50	1.50	1.45	1.80	1.90
Mean[b] latency	*1.93*	*1.92*	*1.72*	*1.67*	*1.58*	*1.54*	*1.91*	*1.95*

[a] All latency measures in msec rounded to 0.05 msec.
[b] Differences as a function of ear are not significant, differences as a function of stimulus level are significant: $P<0.01$ $F(3, 40)=13.34$

Research Paper F.P.L. 17 1964) This was accomplished by assuming an asymptotic value at 1.4 msec for any N_1 latency The data were then fitted by minimizing the variance with a curve given by the general formula ln (latency − 1.4) = $bI+K$ where I = stimulus level in peak dB SPL. b and K are constants.

This relationship is also plotted in Fig. 4 and is given by latency (msec) = $1.4+24.85e^{-.031I}$ The reduction in variance with reference to this line is highly significant ($P<.001$ F (1 99) = 146)

The dashed lines in Fig 4 represent normal bounds established by assuming that the total residual about the regression line was normally distributed. These bounds thus represent the 90% points of a normal distribution. It is to be noted that only seven of the 101 runs yielded latencies outside of these bounds.

DISCUSSION

The electrode arrangement used in our studies provides a simple yet effective means for obtaining human APs without the necessity of minor surgical procedure or anesthesia Normal subjects who participated in these studies reported only minor discomfort during placement of the active electrode

The use of a silver/silver chloride contact and a saline-soaked pledget of cotton reduces problems of electrode contact saline of the pledget and the saline wetting the canal serve as an electrode rather than a small metal-to-skin connection Therefore, slight movement of the electrode probe does not produce a contact breakage.

Note that we have chosen to disregard the amplitudes in determining a so-called input-output function for normals. We feel that the N_1 latency provides the most reliable index of response since this measure is relatively insensitive to electrode position and the N_1 component is most easily distinguished in the tracings we have obtained from our subjects Further we feel that the latency measure of N_1 will suffice to distinguish between normal hearing, conductive losses and sensorineural disorders. In pilot data (Ellis, In progress) conductive losses show a latency function that approximates the normal that is, in the descriptive formula latency = $a+Ke^{-bI}$ K and b are similar in normals and conductive losses The asymptotic value of latency on the other hand, increases beyond the 1.4 msecs estimated for our normal population. Thus a simple shift to the right occurs for the entire latency-intensity function In sensorineural losses, K and b

differ from normals, the phenomenon of recruitment possibly being reflected in APs. The asymptotic constant a in the extreme, closely approximates 1.4 msec. These data for known disorders of hearing constitute trends but represent too little information to permit generalization at this time.

We are aware that the normal bounds established by assuming a residual that is normally distributed about the regression line is to some extent artificial. One would expect a decrease in the dispersion of normal latencies as stimulus intensity is increased. This, in fact, is what occurs in our data, and in the data reported by Yoshie & Ohashi (1969). This implies that normal bounds can be more accurately established by fitting separate curves to the upper and lower limits of the normal latency versus stimulus data. It is interesting to note that our descriptive regression function matches Yoshie & Ohashi's arithmetic averages for 5 normal subjects almost exactly.

Yoshie & Yamaura (1969) report recording CPs by averaging techniques in both conductive and sensorineural loss patients, and have shown that amplitude versus intensity functions serve to differentiate between these conditions and normal hearing. Yoshie & Ohashi (1969) also report that similar differentiations can be obtained by latency measures of N_1 elicited by a click. We support this latter observation and suggest that AP recordings may be preferable to CP recordings for making these types of comparisons. AP data are less susceptible to contamination from coupling of electrical energy since their *form* is relatively independent of the applied stimulus provided onset, or rise time, is rapid enough to assure synchronous discharge of a group of afferent fibers. Either tone bursts or clicks can be employed to obtain AP's. CPs, on the other hand, are difficult to specify unless pure tones are employed. Since coupled energy from the stimulus apparatus will have the same periodicity it is often difficult to determine that a low level CP is not artifact.

Both CPs and APs suffer from the limitation that responses recorded from the promontory round window or ear canal are heavily weighted toward reflecting activity of the hair cells and/or afferent fibers of the basal end of the cochlea. Thus, low frequency conductive losses (e.g., stiffness tilts) may not be reflected in AP data. Sensorineural losses, on the other hand, almost always involve basal turn or high frequency hair cell and afferent fiber activity since basilar membrane mechanics preclude total low frequency sensorineural loss without concomitant basal turn pathology.

CONCLUSION

We believe that recordings of human acoustic nerve potentials by a totally non-surgical technique such as ours provides an effective adjunctive means for auditory assessment in many patients. Further we feel that N_1 latency versus stimulus level curves can provide a measure which will serve to aid the clinician in the differential diagnosis of hearing disorders. These tests can be accomplished quickly and with a minimum of patient discomfort and preparation. Results are independent of subject alertness or sophistication and require little cooperation beyond the ability to lie quietly for a few minutes.

ZUSAMMENFASSUNG

Eine nicht chirurgische Methode für Registrierung von menschlicher akustischer Nerv-Potenzialität der tympanischen Membran wurde beschrieben. Daten von 18 Patienten mit normalem Gehör wurden studiert und eine mathematische Beziehung zwischen stimulierender Intensität und Latenz der N Komponente von dem akustischen Nerv aufgestellt:

1.4 + 24.85 − .051 Intensität.

Eine mögliche Anwendung dieser Beziehung als eine Referenz für eine Diagnose bei Hörstörungen wurde diskutiert. Wir glauben, dass das Registrieren der akustischen Nerv-Potenzialität der tympanischen Membran ein effektives zusätzliches Mittel bei der Abschätzung der Hörbeschwerden vieler Patienten sein konnte. Weiterhin glauben wir dass Vergleichskurven zwischen der N Latenz und dem Stimulus-Niveau ein Hilfsmittel für den Kliniker in der Differenzialdiagnose für Hörstörungen schaffen werden. Registrierungen der tympanischen Membran können schnell gemacht werden ohne bei dem Patienten

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B. V	1.90	2.05	1 60	1.90	1.55	1.65	1.85	2.05
V M	1 75	1 75	1 60	1.50	1 45	1 45	1 75	1 75
R. M.	1 75	1 90	1.60	1.50	1.50	1 45	1.80	1.90
Mean[b] latency	1.93	1 92	1 72	1.67	1.58	1.54	1.91	1.95

[a] All latency measures in msec rounded to 0.05 msec.
[b] Differences as a function of ear are not significant differences as a function of stimulus level are significant: $P<0.01$ $F(3\ 40)=13.34$

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HYDROLYTIC ACTIVITY OF THE PERILYMPH IN OTOSCLEROSIS

A Preliminary Report

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(Received October 1 1971)

Abstract In this study a preliminary report is given of enzymatic studies of the perilymph from otosclerotic patients. Two methods were used. Firstly an enzymatic dissolution of a gelatin film coating was used as a screening method. This method showed hydrolytic ac tivity in 75% and a remarkably close correlation to the evolution of the perceptive hearing loss. Secondly to identify the different enzymes, Uriel & Avrameas micro-electrophoretic method was used, and a high activity of especially acid phosphatase, collagenase and chymotrypsin was demonstrated. In this study there was also a striking correlation of hydrolytic activity to the development of the perceptive hearing loss. It is suggested that these enzymes play a major role in the progressive inner ear disease in otosclerosis.

The search for a pathophysiological back ground which can elucidate the inner ear involvement which is part of the picture in many cases of otosclerosis began very soon after the disease was described.

As early as in 1911 Siebenmann spoke of toxic products" of metabolism, resulting from inflammatory processes, which could act on the organ of Corti via the perilymph or endolymph. Wittmaack (1919) talked about acids" released from the otosclerotic focus. More recently Altmann et al. (1966) put forward the hypothesis that the sensorineural elements were damaged by substances" released from the otosclerotic bone or possibly from an abnormally functioning stria vascularis into the labyrinthine fluids. This clearly shows that no progress on this particular point has been made during the last 60 years. All the explanations which have been put forward appear to have the same purely verbal" content.

The problem of enzymatic study of the perilymph in otosclerosis has always been hampered by both the small amount of fluid avail able and the lack of micro-methods. Further more, pools of perilymph samples cannot be used in such studies as this precludes valuable biochemical and clinical comparisons.

To solve these difficulties we have used two methods in our enzymatic studies of the perilymph from patients with otosclerosis:

1) a modification of the method described by Adams & Tuqan (1961) in which proteolytic activity can be demonstrated by the dissolu tion of a photographic film coating. This is a good screening" method, which can even be quantified to some extent but it is obviously non-specific.

2) the micro-electrophoretic method de scribed by Uriel & Avrameas (1963 1964 *a b*) which makes it possible to define the nature of the enzyme by combining two methods, the

This investigation was aided by grants from l'Association pour la Recherche Medicale Francaise (Paris) and from the Rask-Ørsted Foundation (Copenhagen).

substrate specificity and the migration of the enzyme after 90–120 minutes electrophoresis.

ad 1) *Enzymatic dissolution of the gelatin film coating*

We were able to study 92 samples of perilymph from patients with otosclerosis. These samples were taken at the time of operation (stapedectomies) using a thin plastic tube. The volume of the samples ranged from around 10 to less than 3 microlitres, with the great majority in the range 3 to 5 μl. The removal of such a volume appears to be safe and does not affect the function of the inner ear

The perilymph was immediately placed upon the sensitive gelatin surface, which had been exposed to light. The microdrops were carefully deposited near a mark cut out in a corner of the film and a control of physiological saline buffered at pH 7.2 was deposited near the opposite corner of the film This positioning was constant, so that both the perilymph and the control could be easily checked.

RESULTS

The examination of the perilymph in 92 samples has given the following results.

(a) 35% of the samples caused a complete dissolution of the gelatin coating and these were considered as strongly positive (*b*) 40% showed a positive result, which implies that the gelatin coating showed evidence of dissolution and appeared much thinner than the normal, but the disappearance of the coating was incomplete Translight examination or even spectrophotometry in monochromatic light are useful to ascertain these results (*c*) finally 25% of the samples appeared devoid of any hydrolytic activity and gave a result comparable to the faint halo left by the control drop of physiological saline in the opposite corner of the film.

These results would seem to give a rough and amplified indication that there is some sort of hydrolytic activity related to the development of otosclerosis, even though we were un to establish any correlation between the p ence of the hydrolases and the involvemen the inner ear (progressive perceptive hea loss)

Correlation between activity of perilymph hydrolases and audiometric evolution of th disease

These results are shown in Table I This result of a double-blind test made by tw us. A selection of 50 of the photographic fi 25 with evident hydrolytic activity shown b complete dissolution of the gelatin coat and 25 with the slightest activity were ch by one of the authors. Another author w out knowledge of the above selection, stu the clinical history and the audiometric cu of each of the 50 patients.

As almost all patients are obliged to wait 2 or 3 years before they come to operati and as they attend at intervals of 6 mo during this period for checks of their au grams, we established the following categor based on the changes in the bone-conduct curve for the three conversational frequenc

severe (++) was defined as a fall of m than 20 dB in 2 years before the operat
moderate (+) was defined as a fall from to 20 dB and
none (0) was used if there were no changes a fall of 5 dB.

The audiometric examinations were alw made with the same audiometers, which carefully calibrated every week. Such prec technical conditions justify the definitions have used.

The main results are shown in Table I a were as follows.

Cases with high hydrolytic activity in the pe lymph

Of 25 cases one was discarded because t clinical history was too short (6 months). the remaining 24 only 3 did not exhibit a f of the bone-conducting curves. On the co trary 21 showed an evident fall either in t

Table I *Correlation between the hydrolytic activity of the perilymph and the evolution of the bone-conducting curve for the three conversational frequencies as demonstrated by a double-blind technique*

Total 25 cases	High hydrolytic activity in the perilymph				Total 25 cases	No hydrolytic activity in the perilymph			
		Quantity of the samples calculated from the diameter of the drops					Quantity of the samples calculated from the diameter of the drops		
Case number	Audiometric findings	10–5 μl >5 mm	5 to 3 μl 5 to 3 mm	3 μl <3 mm	Case number	Audiometric findings	10–5 μl >5 mm	5 to 3 μl 5 to 3 mm	3 μl <3 mm
11285	+ +				11298	0			
11292	+ +				11299	[illegible]			
11297	+ +				11318	+			
11306	+				11323	0			×
11312	0				11337	0			
11316	+				11340	0			
11320	+ +				11343	0			
11322	+ +				11345	[illegible]			
11325	+ +				11347	0			
11327	+ +				11349	[illegible]			
11335	+				11372	Min. o. aplas.			
11351	0				11378				×
11368	+				11384	+ +			
11376	+ +				11399	0	×		
11386	+				11406	0			×
11388	+				11410	0			
11402	+ +				11421	0			
11404	+ +				11425	0			
11414	+ +				11430	0			×
11423	+				11453	[illegible]		×	
11464	+ +				11458	0			
11525	+				11521	0			
11542	0				11529	Paget 0			
11549	Less than 6 months				11535	0			
11551	+				11545	0			

range we have defined as severe (12 cases) or moderate (9 cases)

Cases with no hydrolytic activity in the perilymph

Of these 25 cases, 2 were discarded (or rather could be considered as controls) since the analysis of their histories revealed that one was a minor aplasia and the other a Paget's disease (this was due to the use of a double blind technique). Of the remaining 23 only 3 had a falling audiometric curve, one of these in the range defined as severe.

It is striking that the positive and the negative correlations, which are 88% and 86% respectively would seem to be well established on the basis of these 50 cases and it *appears beyond doubt that the rate of cochlear degeneration is a direct function of the hydrolytic activity exhibited by the perilymph fluid in these patients with otosclerosis.*

Statistical analysis of these results showed that this difference was highly significant ($p <$ 0.001 Fisher's exact test).

Many other correlations were analysed, but they do not exhibit such characteristic directness as the one described above. Using quite different methods of study Shambaugh (1966) found that in 73% of 96 patients who had undergone fenestration of one ear and who were followed for 17 to 23 years, there was a significant increase in the sensorineural com-

substrate specificity and the migration of the enzyme after 90–120 minutes electrophoresis.

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Correlation between activity of perilymph hydrolases and audiometric evolution of the disease

These results are shown in Table I. This is a result of a double-blind test made by two of us. A selection of 50 of the photographic films, 25 with evident hydrolytic activity shown by a complete dissolution of the gelatin coating, and 25 with the slightest activity were chosen by one of the authors. Another author without knowledge of the above selection, studied the clinical history and the audiometric curves of each of the 50 patients.

As almost all patients are obliged to wait for 2 or 3 years before they come to operation, and as they attend at intervals of 6 months during this period for checks of their audiograms, we established the following categories, based on the changes in the bone-conducting curve for the three conversational frequencies:

severe (++) was *defined* as a fall of more than 20 dB in 2 years before the operation;
moderate (+) was defined as a fall from 10 to 20 dB and
none (0) was used if there were no changes or a fall of 5 dB.

The audiometric examinations were always made with the same audiometers, which are carefully calibrated every week. Such precise technical conditions justify the definitions we have used.

The main results are shown in Table I and were as follows.

Cases with high hydrolytic activity in the perilymph

Of 25 cases one was discarded because the clinical history was too short (6 months). Of the remaining 24 only 3 did not exhibit a fall of the bone-conducting curves. On the contrary 21 showed an evident fall either in the

Table I *Correlation between the hydrolytic activity of the perilymph and the evolution of the bone conducting curve for the three conversational frequencies as demonstrated by a double-blind technique*

Total 25 cases	High hydrolytic activity in the perilymph				Total 25 cases	No hydrolytic activity in the perilymph			
		Quantity of the samples calculated from the diameter of the drops					Quantity of the samples calculated from the diameter of the drops		
Case number	Audiometric findings	10–5 µl >5 mm	5 to 3 µl 5 to 3 mm	3 µl <3 mm	Case number	Audiometric findings	10–5 µl >5 mm	5 to 3 µl 5 to 3 mm	3 µl <3 mm
11285	+ +				11298	0			
11292	+ +				11299	0			
11297	+ +				11318	+			
11306	+				11323	0			
11312	0				11337	0			
11316	+				11340	0			
11320	+ +				11343	0			
11322	+ +			x	11345	0			
11325	+ +		x		11347	0			
11327	+ +				11349	0			
11335	+				11372	Min. o. aplas.			
11351	0				11378	+			
11368	+				11384	+ +			
11376	+ +				11399	0			
11386	+				11406	0			
11388	+				11410	0	x		
11402	+ +				11421	0			
11404	+ +				11425	0			
11414	+ +				11430	0			
11423	+				11453	0		x	
11464	+ +				11458	0			
11525	+				11521	0			
11542	0				11529	Paget 0			
11549	Less than 6 months				11535	0			
11551	+				11545	0			

range we have defined as severe (12 cases) or moderate (9 cases).

Cases with no hydrolytic activity in the perilymph

Of these 25 cases, 2 were discarded (or rather could be considered as controls) since the analysis of their histories revealed that one was a minor aplasia and the other a Paget's disease (this was due to the use of a double blind technique). Of the remaining 23 only 3 had a falling audiometric curve, one of these in the range defined as severe.

It is striking that the positive and the negative correlations, which are 88% and 86% respectively would seem to be well established on the basis of these 50 cases and it appear beyond doubt that the rate of cochlear de*generation is a direct function of the h*ydro*lytic activity exhibited by the perilymph* f*ound in these patients with otosclerosis*

Statistical analysis of these results sh that this difference was highly significant (p < 0.001 Fisher's exact test)

Many other correlations were analy they do not exhibit such characteristic ness as the one described above. Using different methods of study Shambaugh (1 found that in 73% of 96 patients who ha dergone fenestration of one ear and who followed for 17 to 23 years, there was a si nificant increase in the sensorineural

ponent of the hearing loss in the unoperated ear

Owing to the unspecific character of the enzymatic technique used such results, even though they clearly demonstrate the reality of an hydrolytic activity and its strong correlations with the perceptive hearing loss, which is part of the clinical picture in many cases of otosclerosis, cannot give any precise indication of the enzyme (or enzymes) involved. We have therefore made the following enzymatic studies.

ad 2) *The hydrolytic enzymes in the inner ear* The use of the micro-electrophoresis technique (Uriel & Avrameas 1963 1964 *a b*) makes it possible to demonstrate the hydrolytic enzymes of the perilymph. No details of the technique will be given here. The perilymph samples were either used immediately after they were taken or else rapidly frozen and stored at −25 C. The amount of the samples ranged from 3 to 5 μl. Using the Uriel & Avrameas technique this amount permits a micro-electrophoresis on each of the samples such that the enzymatic and clinical correlations, described above, are possible.

Up to the present following enzymes have studied in 60 samples of perilymph taken patients with various types of otosclerosis:

Group I trypsin, elastase desoxyribonuclease carboxypeptidase B cathepsin

We have never found any signs of activity of the above mentioned enzymes in the perilymph. But negative results should never be considered as definitive, and in the present study these results may be due to the fact that each of the enzymes of this group has been studied in only 3 to 5 cases.

Group II acid phosphatase collagenase, ribonuclease, chymotrypsin.

We found activity of these enzymes in the perilymph, and it may be warranted to make some comments about these positive findings.

Acid phosphatase The substrate we used to demonstrate the activity of this enzyme was the sodium salt of Naphthol AS diphospho acid with the pH kept at 4.8. This enzyme i transphosphorylase and has no direct hyd lytic activity but it is known to take part the lysis of the bone which is involved in t development of the active otosclerotic foc It probably acts on the crystalline part of t bone, preparing the enzymatic attack of t protein moiety of the bone It is interesting note that we have already described the e istence of this enzyme using electron mic scopy and cytochemical studies, as taking p in the constitution of the otosclerotic foc through lysosomal action (Chevance et a 1969 1970) and it is a good example of t fact that the enzymes may leak from a mo or less distant otosclerotic focus, penetrate t capsule and reach the fluids of the inner ea

Collagenase This enzyme is very strong hydrolytic. The substrate used was a soluti of collagen extract (Sigma), 30 mg to 10 ml a tris buffer pH 7.4 A complete discussion the collagenolytic activity is beyond the sco of the present publication, and will be given a subsequent paper But we must point o that when there was collagenolytic activity the samples thus was always high (Fig. 1) a that the number of cases in which collagen was found (19 ears) although still insuffici for statistical analysis, seems in good accor ance with the number of cases in which t gelatin film coating technique had previou revealed an activity i.e. about 75% It is ve probably one of the enzymes which is r sponsible for the findings reported in the fir part of this paper as it attacks undenatur collagen and we have verified that commerc collagenases, which is certainly different, di solves the film coating.

Furthermore in contrast to the high conte of collagenase activity in the perilymph o these patients, we were unable to demonstra any activity in the serum of the same patien

The importance of such a finding, as a bio chemical explanation of the perceptive hea ing loss in the evolution of some cases of oto sclerosis, is emphasized by the fact that in fa

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Les auteurs pensent que certaines de ces enzymes jouent un rôle capital dans la constitution de la surdité de perception qui caractérise l'évolution d'un grand nombre de cas d'ostospongiose.

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conditions. If a pinna function were being disrupted then both standard and modified ear muffs would cause the same degree of performance impairment and further would impair response to white noise signals even more than response to tonal signals compared with normal conditions because of the peculiar effectiveness of the pinna (in theory) in handling complex stimuli. In the second experiment, *Ss* listened to 1 kHz tone and white noise signals in normal, standard earmuffs and earplugs conditions. If attenuation were the cause of the problem then performance for both signal types would be impaired compared with normal conditions (the earmuffs condition being included to act as a comparative control)

EXPERIMENT I

Method

The method used in both experiments was similar to that used by Atherley & Noble (1970). The main hypothesis to be tested in the first experiment was that localization decrement while earmuffs are worn is due to distortion of interaural differences by conduction of sound across the connecting headpiece.

Subjects. Fifteen first year psychology students were used as *Ss* in this experiment. None had had experience of directional hearing experiments nor were they accustomed to using ear protection.

Stimuli. A 1 kHz pure tone and broad-band white noise, both at 20 dB SL, were used as stimuli.

Apparatus. To test localization ability in the horizontal plane, signals were presented diotically from one of six loudspeakers arranged relative to a seated *S* as shown in Fig. 1 Signals were generated by the oscillator of a Peters precision audiometer (Model AP 5) with output through a selector switch to one of six loudspeakers mounted 60 degrees apart on the circumference of a circle of radius 54 inches. The loudspeakers were

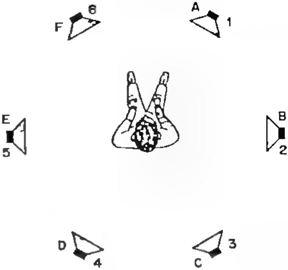

Fig. 1 The positions of the six loudspeakers.

acoustically balanced so that at an equal distance from each the sound pressure level of a 1 kHz tone did not differ by more than 1 dB The loudspeakers were 45 inches from the floor of the room so as to be level with a seated *S* Head movements were not physically restricted. Instead the *S* rested the back of his head on a small metal bar and throughout the experiment was repeatedly instructed not to move his head. The bar was adjustable so that each *S*'s ears would be in a direct line between the two lateral loudspeakers and was small enough not to impede the pathway of signals from lateral and posterior sources.

A set of standard earmuffs of commercial manufacture was used. For the 15 *Ss* tested it was found that the mean attenuation by the earmuffs of a 1 kHz tone was 30 dB and the attenuation of white noise was 36 dB Air-conduction, pure tone free-field audiograms were determined in a further six *Ss* in normal and standard muff conditions and it was found that the earmuffs attenuated increasingly with rising frequency with a maximum of 43 dB at 3 kHz and above A set of modified muffs was also used. These muffs were held on the head independently of each other by *S*. They were the same as the standard muffs but without the connecting

headband. The *S* retained the modified muffs by placing his fingertips on plastic bolts attached to the centre of each muff and held his arms close to the sides of his body in order not to impede signals from the loudspeakers. The *Ss* were able to maintain constant pressure on the modified muffs for a few minutes (sufficient for the experimental trials to be run). Each *S* judged the amount of pressure required by reference to the standard muffs. A check on the attenuation of the modified muffs told *E* whether the equivalent pressure was being exerted on the modified muffs to make them comparable with the standard muffs. None of the *Ss* reported difficulty in this part of the experiment.

Procedure Absolute threshold for both signal types was determined in normal conditions and in standard and modified muffs conditions. For this test use was made of the loudspeaker judged the quietest by *S*. In the localization test there were 30 presentations, in random order of the tone or the white noise in one of the three aural conditions. This was followed, after a rest period, by 30 presentations, again in random order of the other signal type. The order of aural conditions was varied with each new *S*. Each loudspeaker was used five times in a group of presentations. After a signal was presented, *Ss* responded verbally by reference to a chart (similar to the figure) showing the loudspeaker positions labelled 1 to 6. The *Ss* were instructed to fixate the chart, to not move their heads and if unable to make a decision, to say so rather than guess. In the latter cases the response was recorded as "nil" and in the tables of results these "nil" responses account for inconsistencies in the column totals. Rest periods were allowed between each stimulus group.

Results

Objective locations of the signal have been termed A, B, C, D, E, and F. Subjective locations have been termed 1, 2, 3, 4, 5 and 6. Correct responses are thus A1, B2, C3, D4, E5 and F6. Results have been presente[d in] *terms of the total number of correct respo[nses]* and the total numbers of different types [of] error. Two error types were distinguished, [as] by Atherley & Noble (1970): *contrala[teral]* and *front/rear*. In addition to these, a th[ird] type, *adjacent error* was introduced. A c[on]tralateral error is the erroneous location [of] sources on the opposite side of the listener [to] the actual source. This is the most extre[me] type of error which rarely occurs in norm[al] listening conditions. A front/rear error occ[urs] with loudspeakers to the front and rear o[f] and is the erroneous location of the sou[rce] behind when the actual source is in front, [or] vice versa.[1] An adjacent error is the locati[on] of the source at the adjacent loudspeaker [to] the actual one excluding A6, C4, D3, and [F1] which are contralateral errors (Fig. 1).

Table I *Total numbers of correct responses [and] different types of error with tone and white [noise] in normal standard muffs and modified [muffs] conditions*

	Normal		Standard muffs		Modified muffs	
	Tone	White noise	Tone	White noise	Tone	W[hite noise]
Correct	218	407	158	268	154	26[…]
Contralateral	26	0	53	9	53	1[…]
Front/Rear	83	26	119	72	111	7[…]
Adjacent	94	9	94	83	95	7[…]

In each listening condition there were 4[…] presentations of each signal (30 per *S*). T[he] total numbers of different types of respo[nses] to both tone and white noise in norm[al,] standard muffs and modified muffs con[di]tions are shown in Table I. As can be se[en] there were always fewer correct responses [to] the tone than to the white noise and fe[wer] correct responses in standard and modifi[ed] muffs conditions than in normal conditions.

[1] This is a modification of Atherley & Noble's defi[ni]tion (1970). In their study a front/rear error wo[uld] include A1, B1, B3, C2, and so on. In our view the[se] are more properly adjacent errors.

A $15 \times 2 \times 3$ (Subjects × Signal × Listening Condition) analysis of variance of correct responses for each signal type, in normal, standard muffs and modified muffs conditions showed a highly significant main effect of the former with F $(1\ 14) = 73.38$, $p < 0\ 001$ and of the latter F $(2,28) = 37.58$, $p < 0\ 001$ Scheffé's test (Scheffé, 1959) showed that while the difference in correct response between normal and modified muffs conditions was significant ($p < 0.01$) there was a non-significant difference in correct response between standard and modified muffs conditions. This pattern of difference was maintained for all error types. Thus, analysis of variance showed a significant main effect of aural condition for contralateral error with F $(2,28) = 3.33$, $p < 0\ 05$ for front/rear error with F $(2,28) = 11\ 60$, $p < 0.001$ and for adjacent error with F $(2,28) = 8.66$ $p < 0.01$ Scheffé's test again showed a significant difference between normal and modified muffs conditions ($p < 0\ 05$) but not between standard and modified muffs conditions.

The results from Experiment I show that removing the metal strip joining two earmuffs makes no difference to localization performance compared to standard earmuffs conditions. Thus, a possible explanation of the earmuff effect from the viewpoint of the interaural cues hypothesis must be discounted. Clearly some feature intrinsic to the muffs is causing disruption of cues. This finding also means that at this stage no practical suggestions can be made about modifications to ear muff design for safe occupational use.

Whereas the hypothesis about distortion of interaural cues was unsupported, the pinna hypothesis gained ground. This is particularly evident in the different effects of the two types of signal. The *Ss* could locate white noise in normal conditions more accurately than tone. Such would be predicted by the pinna hypothesis. Further the decrement in performance caused by both standard and modified earmuffs appears greater with white noise than with tone (Table I). To test this difference between the two signal types the correct responses of the 15 *Ss* to tone in normal conditions were subtracted from their correct responses to white noise in normal conditions. These differences were then compared with the differences in correct responses between the two signal types in standard ear muffs conditions. The former differences were significantly greater than the latter with t $(14) = 3.625$ $p < 0\ 01$ showing that indeed performance with white noise was more grossly affected by standard muffs than performance with tone. This finding, in the absence of a difference between standard and modified muffs conditions, suggests the impairment of a pinna function by earmuffs.

EXPERIMENT II

Method

The second experiment was designed to test the hypothesis that attenuation, despite adjustment in the level of signals to keep SL constant, is the reason for impairment of localization, or at least contributes to that impairment.

Subjects. Fifteen first year psychology students, again with no experience of localization experiments or hearing protection, were used as *Ss*.

Stimuli A 1 kHz pure tone and broad-band white noise, both at 20 dB SL, were used as stimuli.

Apparatus. Apparatus was the same as that used in the other experiment. Localization was tested in earplug conditions as well as in normal and standard muffs conditions. The earplugs ("glass-down" fibre) were made up by *E* from standard size batches of the material in accordance with manufacturer's instructions and inserted into each *S*'s ear canals. It was found in the 15 *Ss* that the mean attenuation by the earplugs of the tonal stimulus was 14 dB and of white noise was 24 dB. Air-conduction pure tone free field audiograms on another six *Ss* showed that the earplugs attenuated slightly at low frequenci

Table II *Total numbers of correct responses and different types of error with tone and white noise in normal standard muffs and earplug conditions*

	Normal		Standard muffs		Earplugs	
	Tone	White noise	Tone	White noise	Tone	White noise
Correct	214	426	163	296	209	368
Contralateral	28	0	66	11	27	1
Front/rear	101	20	77	76	110	69
Adjacent	96	2	119	53	88	6

and markedly at high frequencies (the average over 0.25 to 1.5 kHz was 10 dB over 2.0 to 8.0 kHz it was 30 dB).

Procedure Absolute threshold was determined in normal, standard muffs and earplugs conditions always for the quietest loudspeaker The procedure then followed that of Experiment I

Results

As in Experiment I there were 450 presentations of each signal type in each listening condition. The total numbers of different types of responses to tones and white noise in normal, standard muffs and earplugs conditions are given in Table II. As can be seen ere were fewer correct responses to tone n to white noise, fewer in standard muffs than in earplugs conditions and fewer in ear plugs than in normal conditions.

A $15 \times 2 \times 3$ (Subjects × Signal × Listening Condition) analysis of variance of correct responses for each signal type in each aural condition showed highly significant main ef fects of both the former with F (1 14) = 512.23 $p < 0.001$ and of the latter with F (2,28) = 19 76, $p < 0.001$ Scheffé s test showed significant differences between normal and earplugs conditions ($p < 0.05$) and between earplugs and standard muffs conditions ($p < 0.01$) An analysis of variance for contralateral errors showed significant main effects for both signal, with F (1 14) = 26.85 $p < 0.001$ and aural condition, with F (2,28) = 11 64 $p < 0.001$ Scheffé s test showed no significant difference between normal and earplugs conditions but a significant difference between earplugs and standard muffs conditions ($p < 0.01$) Analyses for the other two error types showed significant effects of signal (front/rear F (1 14) = 15.31 $p < 0.01$ adjacent, F (2,28) 127 79 $p < 0.001$) and aural condition (front rear F (2,28) = 4 83 $p < 0.05$ adjacent F (2,28) = 39.38, $p < 0.001$) For front/rear errors Scheffé's test showed a significant difference between normal and earplugs conditions ($p < 0.01$) but no significant difference between earplugs and standard muffs conditions. For adjacent errors, the difference between earplugs and standard muffs conditions was significant ($p < 0.01$) but normal and earplugs conditions did not differ significantly

The pattern of response in standard muffs conditions was as expected from the previous experiment. The pattern of response in earplugs conditions did not differ from normal except in the rise in front/rear error for the white noise stimulus. The earplugs were causing some decrement in localization performance although the nature of that decrement was specific (increase in one type of error) rather than general. In particular the earplugs were not associated with any rise in contralateral error

DISCUSSION

The outcome of the first experiment is relatively clear The question was whether the result of Atherley & Noble (1970) could be due to distortion of interaural differences by the metal headpiece joining two earmuffs or whether it could be due to a reduction of pinna function. The latter explanation was partially supported. Localization was impaired with a white noise stimulus much more than with a tonal stimulus but the impairment was neither severe nor total. Contralateral error did not markedly increase with white noise when earmuffs were worn, as it did with tone

In the second experiment another explan-

tion of the decrement in localization performance, the attenuation hypothesis, was not substantially supported. The only change in localization due to earplugs was an increase, with white noise, in front/rear error Had there been an accompanying increase in adjacent error it could have been concluded that previous results were due, at least in part, to attenuation. But clearly earplugs were giving rise to quite a different response pattern from the usual—a pattern which cannot be explained by any of the three hypotheses. In this case it may be that information used for localization was transformed by the earplugs. Whereas earmuffs give a fairly uniform attenuation of white noise (as evidenced by the free-field audiograms) earplugs attenuate high frequencies much more than low Increasing the signal strength of white noise to combat the attenuation of earplugs will lead, therefore to greater low frequency energy in the stimulus than under normal or muffs conditions. A white noise stimulus in normal conditions would have a greater low frequency content when coming from behind *S* because of the shadowing effect of the pinnae which act to absorb high frequency energy in a complex signal (Nordlund, 1962). Thus earplugs might mimic this function and create the illusion of a rearward source irrespective of the actual direction. Supportive evidence for this conclusion of a transformative function is shown by the number of frontward and rearward responses (the two elements of front/rear error) in earplug conditions for both tone and white noise. With tones in earplug conditions there were 55 frontward and 50 rearward responses. That is to say the proportion was equal, as would be expected. With white noise in earplug conditions there were 23 frontward and 46 rearward responses showing an imbalanced proportion which suggests the type of transformation described.

While this explanation is satisfactory for the results with earplugs, there is no obvious explanation in such terms for the impairment of localization when earmuffs are worn. The results of the experiments ruled out two possibilities (conduction and attenuation) and the error patterns do not suggest any systematic transformation of the above type It is more likely that the decline in accuracy is the result of information *reduction* brought about by the restriction in the function of the pinnae Thus pinna explanation is workable as regards white noise, for Batteau's hypothesis specially concerns complex signals, but as has already been pointed out, his expression of the hypothesis does not allow for a pinna function when a 1 kHz tone as stimulus is involved. It could be, however that the hypothesis is too restrictive and that the pinnae do provide cues for directional hearing for this type of signal. The results of these experiments support such an idea—earmuffs impair directional hearing for both a white noise and a pure tone and there is no apparent explanation for this effect. But, while the results may be taken as supporting information reduction and a pinna function, they are not crucial enough to demand complete acceptance of such a hypothesis. Further research, particularly to study adaptation and decision certainty is seen as necessary to allow a definite conclusion on this issue, for if the information to make a decision has been lost when earmuffs are being worn then adaptation will not occur If on the other hand, the information has been transformed in some way then, with suitable feedback, *S* will adapt.

The question of adaptation is of course crucial from a practical viewpoint. It has emerged in these experiments that earmuffs impair localization quite considerably whereas glass-down earplugs have only a minor effect (increasing those errors which occur frequently in normal conditions anyway) An immediate recommendation, therefore would be the adoption of earplugs rather than earmuffs in circumstances where the "effective noise level" (Atherley et al. 1971 in press) permitted their use without risk of hearing damage. If however people are able to adapt to earmuffs then such a recommendation may not be

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DIRECTIONAL AUDIOMETRY

V *The Influence of Azimuth on the Perception of Speech in Patients with Monaural Hearing Loss treated with Hearing Aids (CROS)*

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Abstract Severe monaural hearing loss up to unilateral deafness cannot be treated with an ordinary hearing aid on the ear concerned. A microphone, however can be placed in the vicinity of the bad ear and the sound transmitted to the external auditory canal of the good ear This form of hearing aid treatment is called, in the literature, "Contralateral Routing of Signals CROS. The present investigation shows that such treatment may be advantageous. Nevertheless, under certain conditions, the treatment may lead to the comprehension of speech being worse than without an apparatus. Individual evaluation of the hearing problems of such patients is essential when considering whether treatment with CROS is to be recommended.

The realization that persons with monaural hearing loss cannot be put on an equal footing with those whose hearing is normal has been subjected for a number of investigations (Wark, 1967 Giolas & Wark, 1967). Earlier articles have described how such patients hear and comprehend speech under various experimental conditions (Tonning, 1971 *b*) and it has been pointed out that from the rehabilitation and audiological point of view such patients fall into two groups (Tonning, in press)

(*A*) Patients having a not too severe monaural hearing loss may be expected to receive benefit from hearing aid on the bad ear (op cit.).

(*B*) Patients having a very severe monaural loss of hearing cannot be expected to benefit by a hearing aid on the bad ear

Friedlander (1961) reported that such patients (group B) could be treated by means of a hearing aid where the microphone was placed near the meatus acusticus externus of the bad ear Impulses from this microphone were transmitted through an amplifier to a bone conductor and thence via the cranium to the good ear This method of treatment has however not been widely used. Wullstein & Wigand (1962) attempted to solve the problem by placing a microphone in the vicinity of the bad ear and transmitting impulses thence, via an amplifier to a telephone, which in turn delivered the sound to the good ear This method has attracted the attention of others and in the literature is often designated Contralateral Routing of Signals" CROS (Harford & Musket, 1964 Harford & Barry 1965 Harford & Dodds, 1966 Harford, 1967). This treatment, which from the purely technical point of view is easy to carry out, seems nevertheless to have its problems: for example, the hearing ear might well be more disturbed by noise when using such a hearing aid than it would be without any apparatus at all. The object of this paper is to attempt to throw light on how such a special hearing apparatus affects the comprehension of speech both without and with noise.

Table I. *The relationship between British Standard 1954 and ISO Standard 1964 for our equipment (earphone TDH 39/MX41AR, 9A coupler)*

The table indicates the number of dB that must be added to the threshold of hearing recorded in British Standard when transferring to ISO Standard

Frequency (Hz)	125	250	500	1000	2000	4000	6000	8000
dB added to hearing loss in British Standard when transferring to ISO Standard	−3.5	−3.7	−2.0	−2.9	−0.2	0.0	−7.9	−5.5

METHOD

In this article the dB reference level is 0.0002 dyne per square centimetre. Hearing loss in dB refers to British Standard 2497–1954. The relationship between ISO-Standard 1964 and British Standard 1954 for our equipment is shown in Table I (see also Whittle & Delany 1966).

For this investigation of the Directional Threshold of Intelligibility (DTI, definition see Tonning, 1971 *a*) in patients with monaural hearing loss both with and without hearing aid, the apparatus and technique of investigation has been the same as described in earlier papers (Tonning, 1970, 1971 *a*, 1971 *b* in press).

In 20 patients with a severe monaural hearing loss the DTI was recorded with the signal loudspeaker reproducing speech in four different positions in the horizontal plane (0° = in front, 90° = to the right, 180° = behind, and 270° = on the left side of the person tested). A series of four tests without background noise were made on each person tested. The experiment was then made against background noise (65 dB white noise) for each of the four positions of the loudspeaker reproducing speech, four positions (0°, 90°, 180° and 270°) of the white noise source were used, giving 16 different combinations of positions of the signal and noise loudspeakers. The dB value of DTI refers to the intensity at the point 0.9 metre from the signal loudspeaker. This point corresponds to the centre of the head of the person examined. This value was controlled by calibrating the equipment without any person in the sound field prior to the testing. The intensity of the white noise was likewise adjusted to 65 dB at this central point.

The DTI values of each person were first determined without the use of a hearing aid. Prior to the tests with the hearing aid, the volume control of the aid was adjusted to an appropriate level by means of conversation with the operator in a room, the conditions being like for all the patients tested.

MATERIAL

As test material 20 right-handed patients were used, 8 women and 12 men from 20 to 71 years of age. The average age was 47.0 years, the median age 46.0 years. Pure tone audiograms were recorded for the frequencies 125, 250, 500, 1 000, 2 000, 4 000, 6 000, and 8 000 Hz, using a Madsen Electronics Audiometer Model 0B 60, calibrated according to British Standards. The hearing loss occurred in the right ear in 10 cases, and in the left ear in the remaining 10 cases. All the good ears had a PTA better than 20 dB hearing level. (PTA i.e. Pure Tone Average: the mean of the hearing levels at the frequencies 500, 1 000, and 2 000 Hz.) The bad ears showed only residual hearing or no measurable hearing at all.

The patients had used their hearing aids for at least 3 months before the tests with hearing aid were made. None of the patients had used other hearing aids before this inves-

Table II. *The mean values of DTI ($\overline{DTI}$) for the 4 different positions of the signal loudspeaker. No background noise. The effect of hearing aid on the DTI is indicated*

Position of signal loudspeaker	$\overline{DTI}$ without hearing aid	$\overline{DTI}$ with hearing aid	Effect of hearing aid on DTI
In front	21.7	19.6	Improvement
Bad ear	26.1	18.6	Improvement
Behind	22.4	20.2	Improvement
Good ear	19.5	18.8	No improvement

tigation started. Of our 20 patients, 19 were supplied with hearing glasses (modified Danavox 620) resembling those described by Wullstein & Wigand (1962), Harford & Musket (1964), Harford & Barry (1965), Harford & Dodds (1966) and Harford (1967).

The microphone was situated in the temple piece on the side where the patient had severely impaired hearing. A lead passed from the microphone through the front of the glasses to an amplifier and a telephone in the temple-piece on the side with good hearing. From the telephone a short polyethylene tube carried the sound to the meatus acusticus externus, but without the tube entering the outer ear. The hearing aid was thus mounted not to amplify but to transmit the sound from one side to the other. As a result the patients did not find the sound from the hearing aid uncomfortably loud. One patient used a behind-the-ear aid with internal telephone (Oticon 560AVC) placed behind the bad ear. The sound was led via a polyethylene tube to the outer opening of the good ear.

DTI without noise, both without and with hearing aid

The DTI values without and with hearing aid were recorded for the various positions of the signal loudspeaker. The mean values for DTI ($\overline{DTI}$) were calculated for the four different positions of the signal loudspeaker and listed in Table II.

Wilcoxon-Test for paired comparisons was used, level of significance 0.05. (Statistics in this article according to Dixon & Massey, 1957, Siegel, 1956. An electronic computer was used, the programs being taken from IBM's System 360 Scientific Subroutine Package (360A-CM-03X) Version III 1968.)

It was found that the DTI with hearing aid was better than the DTI without hearing aid for 3 of the 4 positions of the signal loudspeaker (see Table II).

Table III. *The mean values of DTI ($\overline{DTI}$) for the various combinations of signal and noise loudspeakers both without and with the use of hearing aid*

Position of signal loudspeaker	$\overline{DTI}$ without hearing aid	$\overline{DTI}$ with hearing aid	$\overline{DTI}$ without hearing aid	$\overline{DTI}$ with hearing aid
	Position of white noise loudspeaker: In front		Position of white noise loudspeaker: Behind	
In front	53.0	52.5	52.8	52.0
Bad ear	56.9	52.8	55.8	51.4
Behind	53.3	53.0	53.7	53.5
Good ear	49.2	49.9	49.4	49.9
	Position of white noise loudspeaker: Bad ear		Position of white noise loudspeaker: Good ear	
In front	51.5	53.4	56.1	52.6
Bad ear	54.8	53.5	58.9	52.3
Behind	51.7	53.9	56.6	53.7
Good ear	47.2	51.3	53.5	52.7

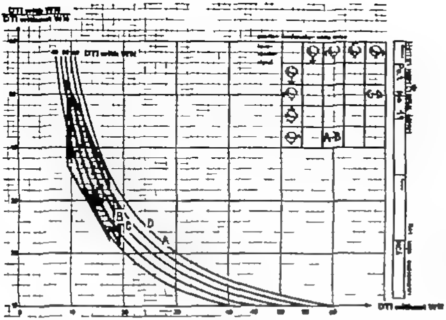

Fig 2 Coordinate system, illustrating the effect of CROS under certain conditions on a patient with impaired hearing in the left ear For further explanation see text.

illustrate how a hearing aid can influence the DTI values under various experimental listening conditions. DTI values of a patient with impaired hearing in the left ear are plotted in the diagram.

1 The signal loudspeaker aimed at the left ear the noise loudspeaker aimed at the right ear

(*a*) Without hearing aid.
DTI without noise
28 dB
DTI with noise
62 dB
Point plotted at A.

(*b*) With hearing aid the same positions of the loudspeakers.
DTI without noise
19 dB
DTI with noise
51 dB
Point plotted at B

Point B lies further to the left in the standard diagram, and is touching the area of the normally hearing 30 standard subjects, while it also lies on an iso-line further down in the coordinate system than point A. These factors indicate that under condition B (with hearing aid) the DTI values in both silence and noise are better than under condition A (without hearing aid) Point B lies on an iso-line going through the area of the 30 normally hearing subjects, indicating that the DTI in noise with hearing aid is not worse than the DTI values of the normally hearing subjects. However the fact that the point A lies to the right of the area of the normal hearing standard group and on an iso-line that is not cutting the area of the normal hearing group indicates that both in silence and in noise without hearing aid, under these listening conditions, the DTI value is poorer than the corresponding DTI values of the 30 normally hearing persons. This does not seem to be the case when a hearing aid is used.

2. Signal loudspeaker aiming at the right (good) ear the noise loudspeaker facing the left (bad) ear

(*a*) Without hearing aid
DTI without noise
21 dB
DTI with noise
51 dB
Point plotted at C.

(*b*) With hearing aid, the loudspeakers in the same positions:
DTI without noise

25 dB.

DTI with noise

64 dB

Point plotted at D

The verticals through points C and D do not cut the area of the normally hearing standard subjects, which indicates that without background noise the DTI values both with and without hearing aid are poorer than the normally hearing standard subjects' values. Point D is seen to lie further to the right and further away from the standard subjects' area than point C, while at the same time point D lies on an iso-line further up in the coordinate system than point C. These facts can be taken to indicate that in situation D (with hearing aid) the DTI both with and without noise, is poorer than in situation C (without hearing aid). Point D lies on an iso-line which does not cut the normal hearers' area, indicating that in situation A (with hearing aid) the patient's DTI is poorer also with noise than that of the normal hearers.

COMMENTS

From Table V and Fig. 2 it can be seen that Contralateral Routing of Signals (CROS) made practicable by a special form of hearing aid, can improve comprehension of speech under certain conditions whilst under other hearing conditions comprehension of speech must be expected to be worse.

This should be taken into account when there is a question of audiological treatment for patients with severe monaural loss of hearing. Will the advantages of CROS outweigh the disadvantages? A person with severely impaired hearing in one ear going about and subjected to noise and speech from varying angles, cannot be expected to derive the same benefit from such a hearing aid as, for example, a chauffeur who cannot hear in the ear turned toward his passengers. Nor could a *school child* be expected to find a CROS apparatus easing the difficulties in all circumstances during teaching: if the bad ear with the microphone is turned toward the class noise which otherwise would not be disturbing may be led to the only ear functioning for hearing. The information which should reach the pupil would then be masked. Here more will be won by placing the pupil in a suitable position than by CROS.

It must be stressed that our experimental listening situation differed considerably from a real hearing situation in everyday life (Tonning, in press). When using the standard diagram in the manner described, it must also be remembered that the deviations in the results of the measurements affects the reliability of the points plotted. If this is remembered together with the fact that the positions of the speakers relative to each other and to the patient also influence the results, it should be possible, by using the standard diagram, to get an impression of the effect of the hearing aid on the DTI under certain conditions. This impression could then be of help in making an evaluation of the effectiveness of the hearing aid treatment.

ZUSAMMENFASSUNG

Schwere Hörschäden auf einem Ohr bis zu einseitiger Taubheit lassen sich nicht durch gewöhnliche Hörapparate am betroffenen Ohr behandeln. Man kann jedoch ein Mikrophon nahe am kranken Ohr anbringen und den Ton zum äusseren Hörkanal des gesunden Ohres übertragen. Diese Art Behandlung mit Hörapparaten wird in der Literatur "Contralateral Routing of Signals (CROS) genannt. Die vorliegende Forschung zeigt, dass eine solche Behandlung günstig sein kann. Unter gewissen Bedingungen kann die Behandlung jedoch dazu führen, dass das Auffassungsvermögen für gesprochene Rede schlechter ist als ohne Apparat. Die Hörprobleme solcher Patienten müssen individuell beurteilt werden, wenn entschieden werden soll, ob eine Behandlung mit CROS anzuraten ist.

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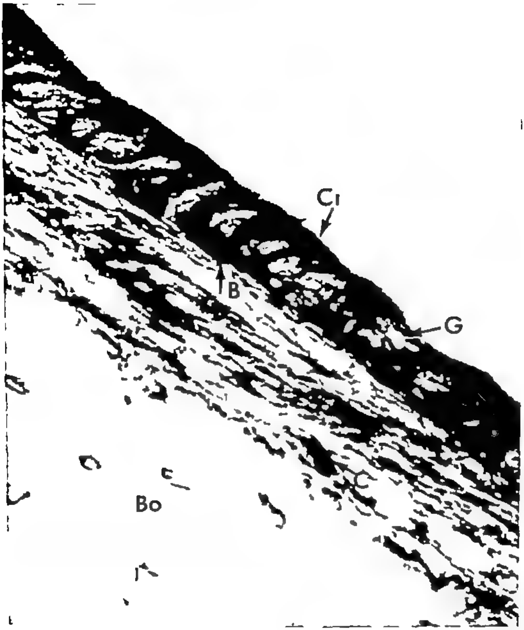


Fig 1 Guinea pig. Strong activity of malic dehydrogenase is seen mainly in the supranuclear cytoplasm of the ciliated columnar cells. High enzyme activity is also present in the basal cells (*B*) and some connective tissue cells (*C*). *G* goblet cell, *Ci* cilia, *Bo*. bone. ×250

an overdose of ether and their temporal bones were immediately removed *in toto* Except for oxidative enzymes they were fixed in 4% neutral formol calcium solution for 24 hours at 4 C. Then they were decalcified in a 10% buffered solution of EDTA for 5–14 days at 4 C (Balogh, 1962) Human temporal bones were obtained at autopsies from patients who died of automobile accidents and were stored in a refrigerated chamber for several hours after death. Except for oxidative enzymes they were fixed in the same fixative as mentioned above for 24 hours at 4 C. Middle ear mucosa was removed from various parts of the middle ear cleft using an otomicroscope.

The decalcified temporal bones and pieces of middle ear mucosa were frozen mounted and cut serially at 15–20 μ with a rotary micro-

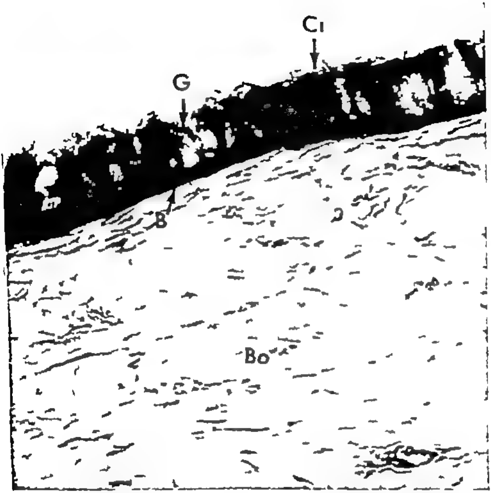


Fig. 2. Cat. Ciliated columnar cells contain a large amount of DPNH diaphorase. Strong enzyme activity is also detectable in the basal cells (*B*). *G* goblet cell, *Ci* cilia *Bo* Bone. ×250.

tome in a cryostat (−20 C) Frozen sections were put on clean coverglasses, thawed slowly and dried at room temperature for $^1/_2$–1 hour Afterwards the sections were incubated in one of the substrate solutions designed for demonstration of the activity of the following enzymes, diphosphopyridinenucleotide diaphorase (DPNH diaphorase), triphosphopyridinenucleotide diaphorase, succinic dehydrogenase, malic dehydrogenase, lactic dehydrogenase, alkaline phosphatase acid phosphatase alanine and leucine aminopeptidases and non-specific esterase

The techniques used for the demonstration of oxidative enzymes were identical to those employed in the inner ear by Nomura & Balogh (1964) The activities of alkaline and acid phosphatases were demonstrated with the methods of Freiman (1954) & Burstone (1958)

For the demonstration of leucine and

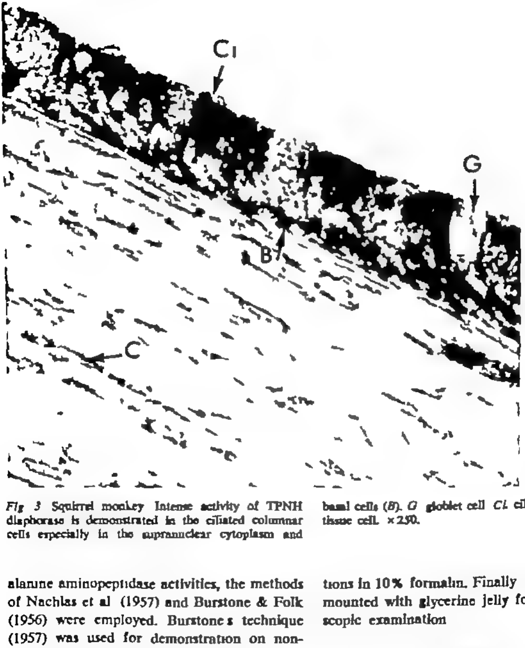


Fig 3 Squirrel monkey Intense activity of TPNH diaphorase is demonstrated in the ciliated columnar cells especially in the supranuclear cytoplasm and basal cells (*B*). *G* globlet cell *Cl* cilia *C* connective tissue cell. ×250.

alanine aminopeptidase activities, the methods of Nachlas et al (1957) and Burstone & Folk (1956) were employed. Burstone's technique (1957) was used for demonstration on non-specific esterase Controls for the histochemical reactions were made by incubating sections in media from which the respective substrate had been omitted All histochemical reactions were terminated by fixing the sections in 10% formalin. Finally the slides were mounted with glycerine jelly for light microscopic examination

RESULT

It was not difficult to distinguish the different epithelial cells even under the light microscope Observations were carried out on the

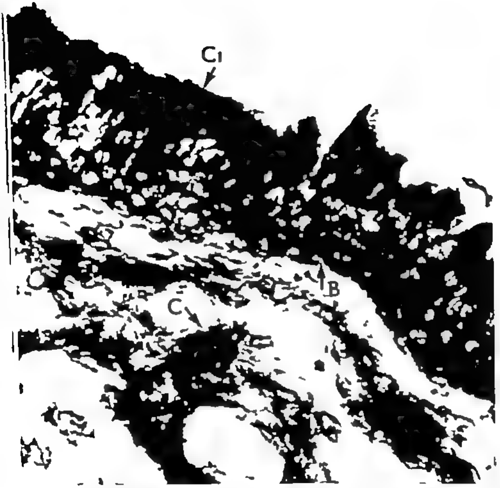


Fig. 4. Human. Ciliated columnar cells reveal strong activity of DPNH diaphorase in the upper portion of cytoplasm. Basal cells (*B*) and some connective tissue cells (*C*) are also positive. *Cl*. cilia. × 400.

cellular epithelial lining and subepithelial layer of the middle ear cavity after the demonstration of various enzymes by means of histochemical techniques. Control specimens showed no histochemical reaction.

Oxidative enzymes

Intense activity of succinic dehydrogenase, malic dehydrogenase, lactic dehydrogenase, DPNH diaphorase and TPNH diaphorase was seen mainly in the supranuclear cytoplasm of the ciliated columnar epithelial cells, which were observed near the tubal openings of guinea pig, cat, squirrel monkey and man, whereas non-ciliated columnar cells appeared to display somewhat less activity of these enzymes than ciliated cells (Figs. 1–4). Goblet cells which were frequently scattered among the ciliated epithelial cells were only moderately or faintly positive. High enzyme activity

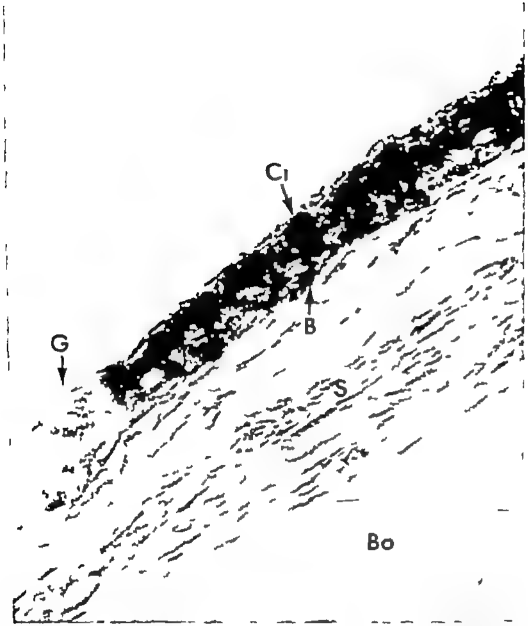
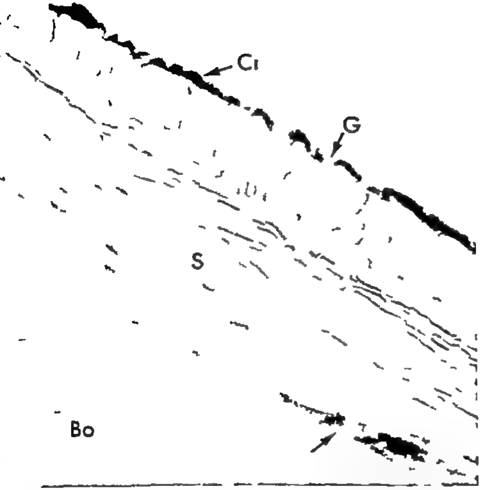


Fig 5 Squirrel monkey Ciliated columnar cells are very rich in acid phosphatase in the supranuclear cytoplasm Considerable amounts of dye granules are also found in the basal cells (*B*). *G* goblet cell, *Ci* cilia *Bo*. bone *S* subepithelial tissue. 250

was also present in the basal cells. Cuboidal cell epithelium showed also moderate activity The flat squamous cells reacted slightly In the simple cell layer there were no special cells which presented marked enzyme activity except cilia bearing cells. Remarkable activity was also seen in the immature fibrocytes or osteoblasts of the subepithelial layer especially near the periosteum of guinea pig and cat. Strong activity was observed in the walls of small blood vessels of all species.

Hydrolytic enzymes

The acid phosphatase enzyme response was seen almost exclusively in the cilia bearing columnar cells, particularly in the supranuclear cytoplasm of squirrel monkey (Fig 5) and man, while ciliated cells of the guinea pig and



g 6. Cat. Strong activity of alkaline phosphatase seen only on the cilia (*Ci*) of ciliated columnar Considerable amounts of azo dye granules are also detectable in the periosteal layer (*arrow*). *G* goblet cells; *Bo*. bone *S*. subepithelial tissue. ×50.

t demonstrated moderate activity Non-liated columnar cells and goblet cells con much less azo dye deposits than ciliated lls. Considerable activity was observed in e basal cells under the tall epithelial cells. us enzyme activity was moderately or faintly 'tive in the cuboidal cell epithelium of all cies. However this epithelium showed oc 'onal positive cells which were probably cilia bearing cells. Squamous cells revealed almost none or only feeble enzyme activity for all species. A strong reaction was also seen in immature fibrocytes and osteoblasts, especially in the periosteal layer of the guinea pig and cat

Alkaline phosphatase activity was not seen in epithelial cells for all species. In the cat, however marked azo dye deposits were ob-

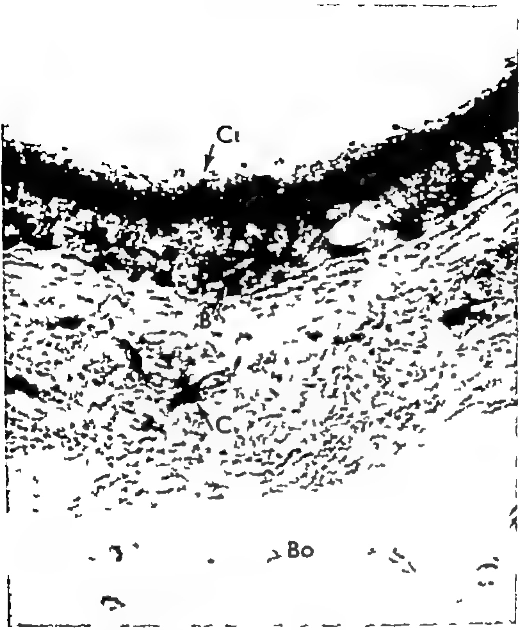


Fig 7 Squirrel monkey Ciliated columnar cells show strong activity of non-specific esterase mainly in the upper portion of the cytoplasm. Basal cells (*B*) and some type of connective tissue cells (*C*) are also positive for the enzyme response. *Ci.* cilia *Bo* bone × 400.

served on the cilia of relatively tall cells which were mainly columnar cells and occasionally cuboidal cells Cilia of other species did not react at all Small blood vessels below the epithelial layer were positive for alkaline phosphatase in all species. Osteoblasts and immature fibroblasts located in the periosteum of guinea pig and cat also contained considerable amounts of dye granules

The non specific esterase response occurred moderately in the cilia-bearing cells and faintly in the other epithelial cells of guinea pig, cat and man However the epithelium of squirrel monkey showed strong activity mainly in the upper portion of ciliated cells (Fig. 7). Non-ciliated columnar cells and cuboidal cells contained moderate amounts of azo dye deposits Flat squamous cells were only slightly colored

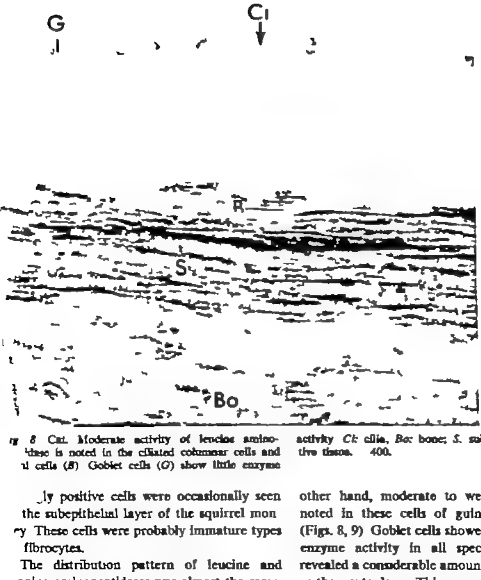


Fig. 8. Cat. Moderate activity of leucine aminopeptidase is noted in the ciliated columnar cells and basal cells (B). Goblet cells (G) show little enzyme activity. Ci: cilia, Bo: bone; S: subepithelial connective tissue. ×400.

...ly positive cells were occasionally seen in the subepithelial layer of the squirrel monkey. These cells were probably immature types of fibrocytes.

The distribution pattern of leucine and alanine aminopeptidases was almost the same. Strong to moderate activity of both enzymes was diffusely distributed in the tall epithelial cells such as ciliated and non-ciliated columnar cells of squirrel monkey and man. On the other hand, moderate to weak activity was noted in these cells of guinea pig and cat (Figs. 8, 9). Goblet cells showed relatively little enzyme activity in all species. Basal cells revealed a considerable amount of dye granules in their cytoplasm. This enzyme reaction product was negligible in low epithelial cells such as cuboidal cells and squamous cells. Marked enzyme activity was noticeable in the subepithelial connective tissues of all species.

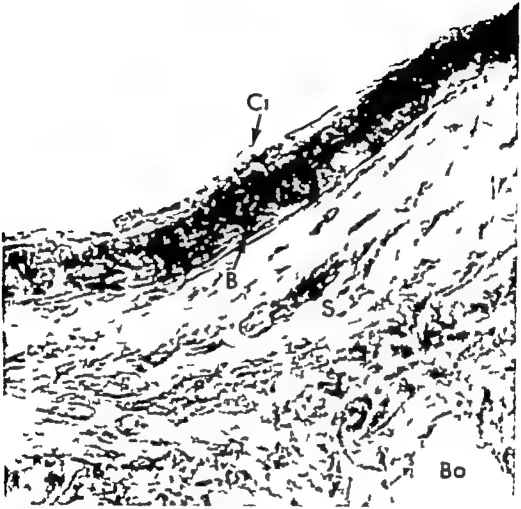


Fig 8 Guinea pig. Ciliated columnar cells and basal cells (*B*) are moderately to weakly positive for alanine aminopeptidase. Considerable activity is also present in the subepithelial connective tissue (*S*). *Ci* cilia; *Bo* bone. ×250.

Guinea pig and cat showed strongly positive reaction in the periosteal layer and moderately positive reaction in the walls of small blood vessels

COMMENT

All enzymes with the exception of alkaline phosphatase showed great activity in the ciliated epithelial cells compared with non-ciliated cells. Cilia-bearing cells have abundant oxidative enzymes whose histochemical reactions result mostly in mitochondrial and partially in extra mitochondrial formation. Cilia-bearing cells are capable of utilizing anaerobic as well as aerobic glycolysis for energy production and can couple hydrogen with molecular oxygen via the cytochrome system. It has been stated that ciliated epithelial cells in the respiratory tract also possess high levels of oxidative enzymes and abundant

mitochondria (Cress et al., 1965 Rhodin, 1966)

Energy derived from processes of oxidative phosphorylation may be utilized by the beating of cilia for evacuating foreign material. It has been generally accepted that acid phosphatase activity can be demonstrated in the lysosome-like structures of various types of cells, by employing combined cytochemical and electron microscopic techniques. Considerable activity of this enzyme in the ciliated cells of the respiratory tract has been described in the trachea and nasal cavity (Hayashi, 1967 Haubrich & Schätzle, 1969) Recently Kawabata & Paparella (1969) have demonstrated lysosome like structures, which are presumably associated with processes involving lysis, in the ciliated epithelial cells of human tympanic mucosa. Rhodin (1966) also reported these structures in the ciliated epithelium of the trachea. The sensory cells of the organ of Corti and vestibular organs also have high levels of acid phosphatase activity mainly in the area above the nuclei (Ishii & Balogh, 1966) However the physiological role of this enzyme in the ciliated cells remains uncertain.

It is of interest to note that intense alkaline phosphatase activity was seen on the cilia of the cat, whereas the cilia of all other species did not reveal any such enzyme activity suggesting obvious interspecies differences. In the inner ear of the guinea pig, stereocilia of the vestibular apparatus also contain a remarkable amount of alkaline phosphatase (Hiraide 1970) The universal appearance of alkaline phosphatase activity on the ciliary structures in these animals suggests some distinct function of this enzyme While the function of the non-specific esterase has not been ascertained, its major localization in various organs suggests that it may be related to regulation of tissue size, detoxication and general lipid-ester metabolism (Ballantyne & Bunch, 1967) Ciliated epithelial cells seem to require much of this enzyme for maintenance of their function because they contain more of this enzyme than non-ciliated epithelial cells.

The specific role of aminopeptidases is not known, but proteolytic enzymes in general have been assigned the role of breaking up protein molecules so that other enzymes involved in protein synthesis may incorporate these breakdown products into new protein molecules. Accordingly the high activity of these enzymes in the tall middle ear epithelium may be related to the presence of a considerable degree of protein synthesis.

These observations emphasize the clearance or drainage role of ciliated cells in the middle ear and suggest means by which they gain energy to perform their task Abundant oxidative enzymes, mainly associated with mitochondria and other hydrolytic enzymes in the ciliated cells, are presumably involved in furnishing energy for ciliary motility

These histochemical studies are also of interest in considering cell secretion possibilities in normal and abnormal (e.g middle ear effusion) conditions. In addition as these cells undergo change in type and structure (metaplasia and hyperplasia) in chronic infectious states, certain cell components and accordingly certain enzymatic and metabolic reactions are activated.

Three different types of secretory cells have been described in the middle ear mucosa of guinea pig and man by Lim et al. (1967 1969)- goblet cells, intermediary cells and dark granulated cells. These cells may presumably have some secretory function in the middle ear cavity under normal circumstances and may serve to lubricate and moisten the cell surface and ciliary tracts. A significantly strong activity of these various enzymes was not displayed in the intermediary cells and dark granulated cells under light microscopy In the future the secretory nature of such middle ear cells will be clarified by more advanced techniques.

ACKNOWLEDGMENTS

We are grateful to Mr Hans Eriksson for his technical assistance and to Mrs Ann Crowell for photography

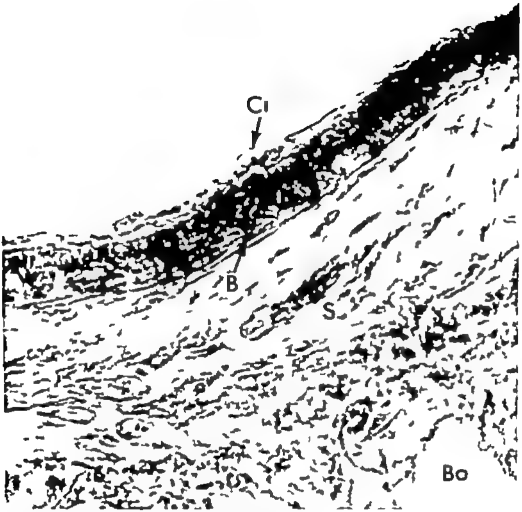


Fig 9 Guinea pig. Ciliated columnar cells and basal cells (*B*) are moderately to weakly positive for alanine aminopeptidase. Considerable activity is also present in the subepithelial connective tissue (*S*). *Ci* cilia. *Bo*. bone. ×250.

Guinea pig and cat showed strongly positive reaction in the periosteal layer and moderately positive reaction in the walls of small blood vessels.

COMMENT

All enzymes with the exception of alkaline phosphatase showed great activity in the ciliated epithelial cells compared with non-ciliated cells Cilia bearing cells have abundant oxidative enzymes whose histochemical reactions result mostly in mitochondrial and partially in extra-mitochondrial formazan. Cilia-bearing cells are capable of utilizing anaerobic as well as aerobic glycolysis for energy production and can couple hydrogen with molecular oxygen via the cytochrome system. It has been stated that ciliated epithelial cells in the respiratory tract also possess high levels of oxidative enzymes and abundant

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OPERATIVE HÖRVERBESSERUNG BEI VERÖDETEM MITTELOHR UND IRREVERSIBEL VERSCHLOSSENER TUBE (1 MITTEILUNG)

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(Eingegangen am 6. September 1971)

Abstrakt · Durch Implantation eines luftgefüllten Hohlkörpers aus Silastic über das runde Fenster gelingt es, bei Patienten mit völlig verödeter Pauke und irreversibel verschlossener Tube einen beträchtlichen Hörgewinn zu erzielen. Die Methodik wird beschrieben und das Ergebnis an [illegible] Beispielen demonstriert.

Ein bisher praktisch ungelöstes tympanoplastisches Problem ist die chirurgische Hörverbesserung bei verödetem schleimhautlosem Mittelohr und gleichzeitigem irreversiblem Tubenverschluß Solche Befunde entstehen als Endstadium einer Otitis media chronica adhäsiva, durch sehr fortgeschrittene Cholesteatombildungen oder als Folge einer Ohrradikaloperation alten Stils mit gleichzeitiger Tubenverödung.

Die bisher publizierten Versuche, eine verschlossene Tube zu ersetzen oder wieder zu öffnen (Armstrong, 1954 u.v.a. — Plastik … Drettner & Ekvall, 1969 — tympano-…illärer Shunt House et al., 1969 — Tubenplastik) setzen voraus, daß eine normale oder doch regenerationsfähige Mittelohrschleimhaut noch vorhanden ist.

Fehlt die Schleimhaut im Mittelohr ganz, so bleibt nur prinzipiell andere Wege zu … Die einfachste Form, in einem solchen Ohr mit noch beweglicher Fußplatte eine vor… hende Hörverbesserung zu erzielen ist die Schaffung einer Phasendifferenz für eintretenden Schall zwischen beiden Labyrinthfenstern durch Abdecken eines Fensters mit einem Watte-Salben-Filz oder mit porösem Kunststoff von außen (Gaudin, 1968). Eine andere Möglichkeit bildet das „künstliche Mittelohr" von Sedláček (1965 1967).

Die Verwendung eines die Schallübertragung modifizierenden Systems, das frei im Gehörgang liegt, hat einige Nachteile. Fremdkörperreiz, Entzündungen oder Verlagerung der Einlage zwingen zu wiederholten Korrekturen bzw Neuanfertigungen. Es sind also keine dauerhaften und nachsorgefreien Lösungen des Problems.

Einen anderen Weg beschritt Gaudin (1968) als er Implantate aus Silikon-Elastomer dem runden Fenster direkt auflegte und sie durch Deckung mit Gewebeautotransplantaten zur Einheilung zu bringen suchte. Das von Gaudin publizierte Implantatverfahren führt in 50–70% zu Hörverbesserungen von 10 dB und mehr (1 Jahres-Ergebnisse). Mißerfolge waren bedingt durch Abstoßung des Implantates (Unverträglichkeit) Verschiebung des Implantats im Einheilungsprozeß und Verlust des Anfangsergebnisses durch Deformierung oder Kompression des Implantates vom umliegenden Gewebe her Der Verfasser bezeichnet die Verbesserung des verwendeten Implantates selbst als wünschenswert.

Wir selbst haben 1967 begonnen, verschiedene Implantate auf ihre hörverbessernde Wirksamkeit zu erproben.

Solche Implantate müssen folgende Forde-

Abb 1 Implantierbarer Silastichohlkörper

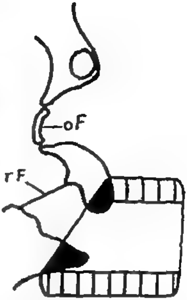


Abb 2 Vertikaler Schnitt durch die mediale Paukenwand. Lage des Hohlkörpers über dem runden Fenster (*rF*). *oF* = ovales Fenster Schwarz: Mit der Fräse entfernte Knochenteile.

rungen erfüllen 1 Sie müssen vom Gewebe optimal toleriert werden und 2. sie müssen akustisch eine optimale Phasendifferenz zwischen beiden Labyrinthfenstern gewährleisten.

Wir erprobten über längere Zeit luftgefüllte Silastichohlkörper verschiedener Form und Größe mit unterschiedlichen Wanddicken. Da alle Plastsubstanzen in dünner Schicht gasdurchlässig sind, bestand das Problem vor allem darin, den Hohlkörper so anzufertigen, daß die physikalischen Verhältnisse beim Übergang der Schallwellen in Richtung zum runden Fenster etwa denen bei einem normalen Mittelohr entsprechen. Andererseits war der Hohlkörper durch Wahl unterschiedlicher Wanddicken so zu stabilisieren, daß er trotz Gasdiffusion durch die dünnen Wandabschnitte hindurch nach außen mit resultierendem leichtem Unterdruck im Inneren nicht kollabieren und damit unwirksam werden konnte

Folgende Lösung hat sich uns bisher am besten bewährt Von einem Silastieröhrchen[1] (Innendurchmesser 1 98 mm, Außendurchmesser 3 18 mm) wird ein 3 mm langes Stück so schräg abgeschnitten daß der kürzeste Wandteil etwa 1,5 mm lang bleibt. Das Röhrchen wird durch Aufkleben von Silasticfolie 500-1[1] mittels Silastic Medical Adhesive Silicone Type A[1] auf beiden Seiten verschlossen (Abb 1) Nach einer Trocknungszeit von einigen Tagen sind diese Hohlkörper sterilisierbar (120 30 min)

Operatives Vorgehen.

In Lokalanästhesie wird unter Bildung eines Sourdille Lappens im hinteren unteren Gehörgangsbereich durch vorsichtiges Abschieben der Weichteile vom Knochen des Gehörgangs, dann vom hinteren und unteren Paukenrecessus der Rand des runden Fensters unter Vermeidung einer Verletzung der runden Fenstermembran ganz dargestellt. Mit einer Diamant Fräse wird das Relief der runden Fensternische so umgestaltet, daß das schräge Ende des Hohlkörpers dem Fensterrand glatt aufliegen kann (s. Abb 2). Der Hohlraum des Implantats liegt dabei über dem *Eingang* in die Fensternische Das Implantat wird dann zur Stabilisierung mit Fascienstückchen um-

[1] Hersteller Dow Corning Corporation, Midland Michigan, USA.

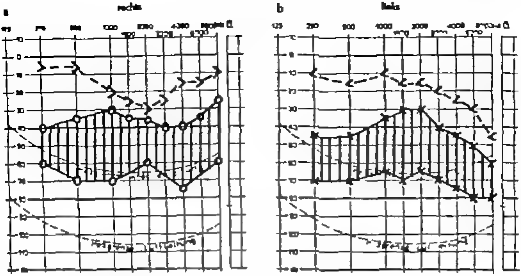


Abb 3 (*a b*) Audiogramme zu den Beispielen 1 u. 2.

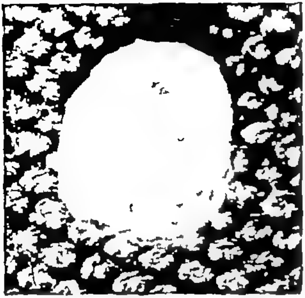
legt und mit einer Lage Fascia temporalis abgedeckt. Abschließend wird das vorher über dem runden Fenster hochpräparierte Gewebe mit bedeckendem verhornendem Plattenepithel auf die Fascie zurückgeschlagen und der Gehörgang mit Penicillin-Gelatineschwamm ausgefüllt.

Die Entfernung des Gelatineschwamms erfolgt nach etwa 2 Wochen. Zu dieser Zeit sind die Wundflächen reizlos verheilt. Das endgültige funktionelle Ergebnis ist nach 2–3 Monaten erreicht.

Am Beispiel von 2 Patienten bei denen der Eingriff vor 20 bzw 22 Monaten ausgeführt wurde soll das Ergebnis solcher Paukenimplantationen, die zu einem funktionellen Typ IV (nach Wullstein) führen, demonstriert werden.

1 N Monika, 26 Jahre alt. Zustand nach radikaler Ohroperation beiderseits wegen ausgedehnter Cholesteatombildung. Die mediale Paukenwand ist auf beiden Seiten zusammen mit der Operationshöhle völlig mit verhornendem Plattenepithel ausgekleidet, die Gehörknöchelchenkette fehlt bis auf die Stapesfußplatte. Die Fußplatte selbst ist bei Betasten beweglich, die Tube obliteriert. Prothesenversuch Provisorische Abdeckung des runden Fensters mit einem Watte-Salben-Filz ergibt wesentlichen Höranstieg. Operation am 12.1 70 rechts: In Lokalanästhesie wird in der obenbeschriebenen Weise das runde Fenster dargestellt. In der Nische findet sich noch etwas Schleimhaut und cholesterolhaltiges Exsudat. Der Schleimhautrest wird vorsichtig entfernt und die Nischenumgebung mit der Diamant Fräse so modelliert, daß das Silastikimplantat mit seinem Hohlraum über dem Fenstereingang liegen kann. Abdecken des Implantats mit Fascie und der hochpräparierten Paukenauskleidung. Glatter Heilverlauf Das Audiogramm (Abb. 3 *b*) zeigt das Ergebnis der Operation 20 Monate später

2. H Elvira, 39 Jahre. Zustand nach radikaler Ohroperation beiderseits wegen ausgedehnter Cholesteatombildung. Pauke und Radikalhöhlen beiderseits komplett mit verhornendem Plattenepithel ausgekleidet. Tube auch nach Präparation des Tubenostiums nicht durchgängig. Prothesenversuch. Guter Höranstieg. Am 12.1 70 Operation rechts in der beschriebenen Weise *Das Audiogramm* (Abb 3 *a*) zeigt das Ergebnis [illegible] Monate nach der Operation.



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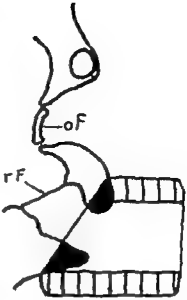

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Folgende Losung hat sich uns bisher am besten bewährt Von einem Silasticröhrchen[1] (Innendurchmesser 1,98 mm, Außendurchmesser 3 18 mm) wird ein 3 mm langes Stück so schräg abgeschnitten daß der kürzeste Wandteil etwa 1,5 mm lang bleibt. Das Röhrchen wird durch Aufkleben von Silasticfolie 500-1[1] mittels Silastic Medical Adhesive Silicone Type A[1] auf beiden Seiten verschlossen (Abb 1). Nach einer Trocknungszeit von einigen Tagen sind diese Hohlkörper sterilisierbar (120 30 min)

Operatives Vorgehen

In Lokalanästhesie wird unter Bildung eines Sourdille Lappens im hinteren unteren Gehörgangsbereich durch vorsichtiges Abschieben der Weichteile vom Knochen des Gehörgangs dann vom hinteren und unteren Paukenrezessus der Rand des runden Fensters unter Vermeidung einer Verletzung der runden Fenstermembran ganz dargestellt. Mit einer Diamant Fräse wird das Relief der runden Fensternische so umgestaltet daß das schräge Ende des Hohlkörpers dem Fensterrand glatt aufliegen kann (s. Abb. 2) Der Hohlraum des Implantats liegt dabei über dem Eingang in die Fensternische. Das Implantat wird dann zur Stabilisierung mit Fascienstückchen um-

[1] Hersteller: Dow Corning Corporation, Midland, Michigan, USA.

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RESULTS OF TYMPANOPLASTY WITH MODIFIED RADICAL MASTOIDECTOMY

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Abstract The results of tympanoplasty combined with modified radical mastoidectomy in the same stage on 266 discharging ears was assessed by various criteria. Prior to the operation 9% of the cases had social hearing, 3–9 months after 47%. The air–bone gap closed to within 0–15 dB in 37% of the cases, within 0–30 dB in 77%. A hearing gain exceeding 10 dB was obtained in 66%. Perforation recurred in 14% of the cases, and 8 ears could not be rendered dry. The results in cholesteatoma were found to be the same as in chronic granulating otitis. The results were identical in cases where the bridge was preserved and in cases where it was removed. There was no major difference between the various types of tympanoplasty with respect to the magnitude of the hearing gain, but the mean postoperative hearing was considerably better after type I–III than after type IV tympanoplasty. The most successful ossiculoplasty proved to be interposition of bone and incus, least successful with interposition of polyethylene. The results in the discharging ears were compared with those in dry ears and were found to be appreciably better in the latter

The object of this paper is to present the results of modified radical mastoidectomy with tympanoplasty in the same stage on a material of ears with chronic discharge—the operative indication being to clear the ear—and to compare with the results of tympanoplasty without mastoidectomy on dry ears in a material where the main object was to improve hearing. The material comprises all tympanoplasties from 1965 to 1970. From the very beginning, therefore, we have been able to utilize the experience from the great pioneer studies (Zöllner 1957 Wullstein, 1960· Proctor 1960· Palva & Pulkkinen, 1960 Pfaltz et al., 1962, Portmann, 1963 Zöllner 1966) and our results will be compared with theirs.

MATERIAL AND OPERATIVE METHOD

The material comprises 266 discharging ears. In the majority of cases the discharge had lasted for years. In 54 cases there was perforation of the pars flaccida, in the remaining cases, of the pars tensa. In 61 cases the perforation was total, in 72 cases large and in 79 cases small. The ossicular chain was intact in only 54 of the cases. In 18 cases the lenticular process was missing, in 134 the long process of the incus, and in 47 cases the entire incus. In 14 cases parts of the stapes were missing and in 87 cases the entire stapes. In 65 cases parts of the malleus and in 19 cases the entire malleus was missing.

Mastoidectomy was done in all the cases. The bony annulus (bridge) was preserved in 107 cases, but greatly narrowed, while in the remaining case it was removed. In the tympanic cavity the granulations and parts of the granulating mucosa were removed. Frequently small pieces of silastic film were inserted on each side of the stapes and in the case of major mucosal defects on the promontory. The various disease states and the ossiculoplasties used will be mentioned under Results. In cases of large and total perforation, temporal fascia was placed on the drum remnant and carried

Table I. *Results of tympanoplasty with modified radical mastoidectomy in 266 discharging ears assessed by various criteria*

Criteria	Before operation *n*	Before operation %	After operation *n*	After operation %
1. Social hearing (0–30 dB)	25	9	125	47
2. Air–bone gap				
0–15 dB	2	1	98	37
16–30 dB	79	30	105	40
> 30 dB	185	69	63	23
3. Hearing gain				
Exceeding 40 dB			4	2
Exceeding 30 dB			22	8
Exceeding 20 dB			85	32
Exceeding 10 dB			174	66
0–10 dB			50	19
No hearing gain			28	10
Deterioration			14	5
4. TI (0–30 dB)	43	16	149	56

across the bridge to the superior epitympanic wall. In cases where the bridge was removed the epitympanum was filled with gelfoam and the fascia was carried in the same way to the superior epitympanic wall. The mastoid cavity was obliterated by a bipartite superiorly pedicled flap of muscle and periosteum (Tos, 1969). The auditory canal was dilated.

RESULTS

The results are based upon the last tone audiogram in the frequency range 500–2 000 cps 3–9 months after the operation and upon speech audiometry stated as the threshold of intelligibility (TI). Table I gives the results assessed by the various criteria.

By disease state there is not much variation in the results (Table II). In particular there is no difference between cholesteatoma and granulating chronic otitis media. Among the cases with a history of resection the majority were previous radical cavities with chronic infection of the middle ear as well as of the cavity. In these cases the middle ear was reconstructed and the cavity obliterated. The group of chronic adhesive otitis relates to patients with chronic suppurative otitis in an adhesive ear with a totally retracted, thin drum remnant and atelectatic tympanic cavity. The tympanoplasty technique was the same as that used in 56 cases of chronic adhesive otitis media on dry ears (Tos, 1971). Bony fixation of the malleus or incus in the epitympanum was found more often in dry ears, viz. in 10 % of the cases with intact ossicular chain (Tos, 1971) than in discharging ears in which it was found in only 7 cases.

The auditory success was calculated as follows. As successes we have classified the 125 patients who attained social hearing, the 70 patients who did not attain social hearing but in whom the air–bone gap closed to within 0–15 dB, the 26 patients who obtained a hearing gain exceeding 20 dB, although they did not attain social hearing or an air–bone gap closure within 0–15. In spite of the modified radical mastoidectomy these patients obtained a good

Table II. *Results in various disease states expressed in per cent*

	No. of cases	Percentages of cases obtaining: Social hearing	Hearing gain exceeding 20 dB	Hearing gain exceeding 10 dB	Air–bone gap 0–15 dB	TI 0–30 dB	Success
Cholesteatoma	130	46	30	67	39	59	[illegible]
Granulating otitis	72	49	31	65	43	53	69
History of resection	19	37	58	58	37	32	76
Adhesive otitis	38	53	3	63	39	[illegible]	64
Bony fixation	7	57	14	71	43	71	71
Total series	266	47	32	65	37	56	69

able III. *Comparison of results (tympanoplasty vs mastoidectomy) in cases where the bony bridge as removed or preserved*

	No. of cases	Postop. hearing	Hearing gain (dB)	Postop air bone gap	Success ( )	Recurrent perf. (%)
ridge preserved	107	36.5	16.0	23.5	68	19
ridge removed	159	36.8	14.1	22.8	70	11

earing gain and are quite pleased with the result. Moreover 13 patients attaining a TI of 30 dB or more are included among the successes. In these cases the hearing improved to more than 30 dB in only a few of the higher frequencies. Within the entire material auditory success was achieved in 69% of the cases (Table II)

In 14 cases (Table I) the hearing deteriorated. In 5 of these cases the perceptive hearing, especially of high tones, also deteriorated, and in 2 of the patients the state was almost anacusis. The mean hearing deterioration in these 14 patients was 21 dB.

Perforations recurred in 14% of the cases. In 11 cases the perforation was the same as prior to the operation, whereas 27 cases had a smaller perforation, as a rule at the edge of the graft. The mean hearing gain in these cases was the same as that in the material as a whole. There was no major difference in the incidence of recurrent perforations between ears with cholesteatoma and ears with granulating suppurative otitis. Eight ears have had constant discharge since the operation, while the others have been dry since the treatment was completed.

It was not attempted to preserve the bony annulus at any price. In the group with cholesteatoma the annulus was preserved and narrowed in 26% of the cases, in 65% of those with granulating suppurative otitis, and in 63% of those with adhesive otitis. The results in the group with a preserved bridge where no better than in the group in which the bridge had been removed (Table III). The results show that too much reserve need not be displayed in removing the bony annulus, especially if this increases the chances of radicalness and facilitates access to the stapedial region and the tubal orifice.

It was invariably attempted to preserve an intact ossicular chain. Indeed, the results were most favourable in type I tympanoplasty the mean postoperative hearing and air–bone gap being considerably better than in the other types (Table IV) The results were poorest after type IV tympanoplasty so that now we are using type III to an increasing extent instead of type IV

The results of using the various ossiculoplasties in type II tympanoplasty (Table V) were best when a piece of bone was interposed between the head of the stapes and the drum or between the head of the stapes and a defective long process of the incus. The results were also fairly good after transposition of the handle of the malleus, but this method was

Table IV *Mean postoperative hearing hearing gain and air–bone gap in the various types of tympanoplasty*

	No. of cases	Postop. hearing	Hearing gain (dB)	Postop. air-bone gap	Success *n*	Success %
Tympanoplasty I	52	27.3	13.1	16.7	41	79
Tympanoplasty II	97	35.6	16.3	23.0	72	74
ympanoplasty III	95	39.6	14.0	25.4	61	64
Tympanoplasty IV	22	46.4	14.5	20.9	10	46

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Bony fixation	7	57	14	71	43	71	71
Total series	266	47	32	65	37	56	69

Table VII *Comparison of results of tympanoplasty on 269 dry and 266 discharging ears expressed in per cent*

	Social hearing 0–30 dB	Hearing gain exceeding 20 dB	Hearing gain exceeding 10 dB	Air bone gap 0–15 dB	TI 0–30 dB
Dry	67	56	87	63	76
Discharging	47	32	65	37	56
Total series	57	44	76	50	67

mean postoperative hearing was 33.0 dB mean hearing gain 19.0 dB Pfaltz et al. (1962) obtained, in 200 type I–IV tympanoplasties on *discharging* ears, a closure of the air–bone gap to within 0–15 dB in 7% as compared with 37% in the present material and a hearing gain exceeding 10 dB in 40% as compared with 66% in the present material. A TI of 35 dB or better was found by Pfaltz et al. in 29% of their cases prior to the operation and in 46% after In the present material a TI of 30 dB or better was found prior to the operation in 16% of the cases and after the operation in 56% (Table I). Portmann (1963) obtained, in a *mixed* series of 275 cases treated by type I–IV tympanoplasty a hearing gain of more than 10 dB in 64% as compared with 76% in the present material. In Zöllner's (1966) *mixed* series of 739 type I–IV tympanoplasties 81% of the cases obtained a hearing gain of more than 10 dB while in 4% the hearing deteriorated. In the present material the corresponding values are 76% (Table VII) and 3% The mean hearing gain in Zöllner's entire series was 17.8 dB, in the present material 19.0 dB. 12% of Zöllner's material had social hearing prior to the operation, 49% after In the present material social hearing was found in 3% prior to the operation, in 57% after

ZUSAMMENFASSUNG

Die Resultate bei Tympanoplastik mit modifizierter radikaler Mastoidektomie in einer Seance bei 266 fließenden Ohren wurden nach verschiedenen Kriterien berechnet. Vor der Operation hatten 9% 3–9 Monate nach der Operation 47% der Fälle soziales Gehör Die Mittelohrkomponente wurde bei 37% bis zu 15 db, bei 77% der Fälle bis zu 30 db geschlossen. Verbesserung des Gehöres von über 10 db wurde bei 66% der Fälle gefunden. Perforation rezidivierte bei 14% der Fälle, und 8 Ohren wurden nicht trocken. Die Resultate bei Cholesteatom waren gleich den Resultaten bei granulierender kronischer Otitis. Die Resultate waren in den Fällen identisch wo die Brücke nicht entfernt und wo sie entfernt wurde. Die durchschnittliche Gehörverbesserung varilerte nicht viel zwischen den verschiedenen Tympanoplastiktypen aber das durchschnittliche Gehör wurde bedeutend besser bei den Typen I III als bei Type IV Ein Erfolg wurde am häufigsten erreicht bei Interposition von Knochen oder Incus, seltener bei Polytan. Die Resultate bei den fließenden Ohren wurden mit den Resultaten bei trockenen Ohren verglichen, wo sie viel besser sind.

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UTRICULAR ABLATION AND DYSEQUILIBRIUM IN SQUIRREL MONKEYS

M. Igarashi, H. Miyata and B R. Alford

From the Department of Otolaryngology Baylor College of Medicine Houston Tex USA

(Received November 15 1971)

Abstract The body equilibrium compensation profile (degree of dysequilibrium, direction of falls, etc.) after unilateral utricular nerve section was investigated in squirrel monkeys. Severe dysequilibrium was observed after this procedure without exception. Complete equilibrium compensation took place three weeks to one month postoperatively The difference in equilibrium function after unilateral utricular nerve section and saccular macula ablation in the squirrel monkey was clearly demonstrated.

The importance of neural discharges from various vestibular end organs in the maintenance of bodily equilibrium in daily life is well known. Since the otolith end organ system is not only a gravity receptor but a linear acceleration receptor as well, its function may be important while the subject is progressively moving. The importance of the macula utriculi this respect has been well discussed (McNally 1955 1956) and investigated by utilizing either destruction or stimulation experiments in many different animal species fish, frogs, snakes, pigeons, rabbits and cats (Versteegh, 1927 McNally 1933 McNally & Stuart, 1942 Sullivan et al., 1957 van Eyck, 1959 Fernández et al. 1959) In the present study using subhuman primates, an attempt was made to investigate quantitatively the contribution of the macula utriculi toward maintenance of bodily equilibrium. The compensation profile after unilateral ablation of this end organ was also studied.

This investigation was supported by National Institutes of Health Research Grant NS-07237 Research Career Development Award 5K03NS38619 and RR-00259

PROCEDURE

The procedure of squirrel monkey rail test has been previously described (Igarashi, 1968; Igarashi et al., 1970) Both the pre and post-operative ability of the squirrel monkey to traverse the rotating rail was investigated. The rail threshold values and the performance profiles, which include percentage and direction of falls, were recorded for analysis.

In the present experiment, all surgical procedures were performed unilaterally on the left ear Intravenous sodium pentobarbital injection (30 mg/kg) was utilized for general anesthesia. A retroauricular atticotomy approach was used. The stapes was removed routinely Depending upon the anatomical factor the anterior superior edge of the oval window was very slightly drilled off for better visualization of the utricular macula and nerve. An extremely fine pick was inserted through the oval window to section the utricular nerve along the anterior bony lamina After sectioning the nerve, slight bleeding was usually noticed. Perilymph aspiration was minimum and special care was taken not to injure other vestibular end organs, especially the lateral semicircular canal crista. The oval window was thereafter sealed with autogenous adipose tissue, the tympanic cavity was filled with gel foam and the incision was closed.

Fourteen subjects were used for utricular nerve section. One subject was excluded because of surgical failure Two other animals

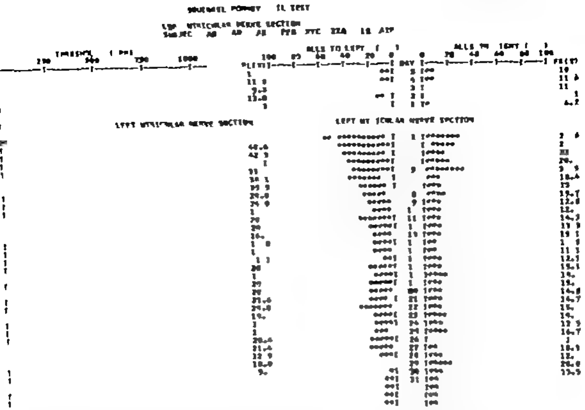

Fig. 1. This computer printout displays the average status of eight squirrel monkey subjects after unilateral utricular nerve section. Asterisks in the left column demonstrate the postoperative condition of rail thresholds. Asterisks toward the left indicate an ataxic condition. Numbers and asterisks in the right column exhibit the postoperative compensation profile which includes the direction and the percentage of falls (number of falls/total number of runs on that day).

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Postoperatively when the subject regained he preoperative rail threshold level for at east three consecutive testing days, the subject as sacrificed by means of intravital cardiac erfusion The temporal bones were removed nd processed according to the standard pre aration procedure for histological investiga- on.

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The average postoperative rail threshold decline in 8 subjects with utricular nerve sec tion was severe, and more than 3 weeks were required for the animals to regain the exact preoperative level, as seen in the computer printout (Fig. 1) Statistical study by *t* test, however showed that the average rail threshold on 13th postoperative day was insignificant at the 0.05 level ($P > 0.05$) when compared with the average preoperative (3 days) rail threshold. To regain the preoperative performance profile status took even longer about 1 month, as seen in the printout.

The shortest time for rail threshold com pensation was found to be 7 days. In the animal with the shortest compensation time, the utric

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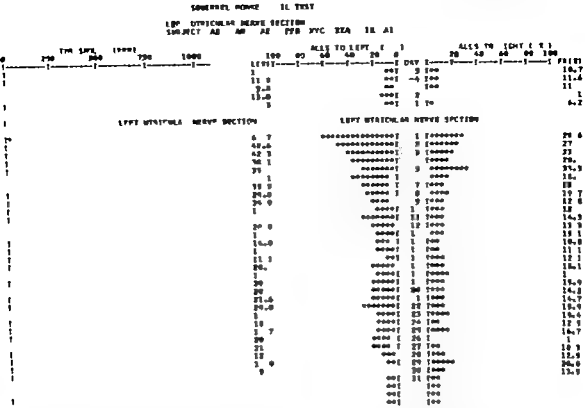

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Fig. 2 (*A*, *B*) Photomicrograph demonstrates histological findings of utricular nerve sectioned side (*A*) and of normal ear (*B*) from same subject. An arrow indicates the site of utricular nerve section. *A* ×60. *B* ×60.

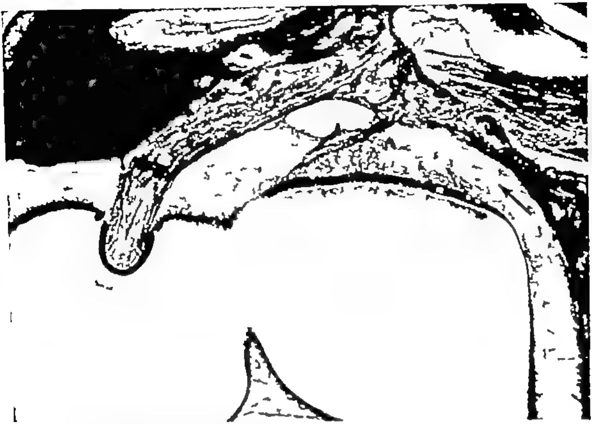

Fig. 3 This photomicrograph exhibits another view of utricular nerve section from different subject. An arrow indicates the location of nerve section. A part of the utricular nerve adjacent to lateral semicircular canal nerve remains. ×70.

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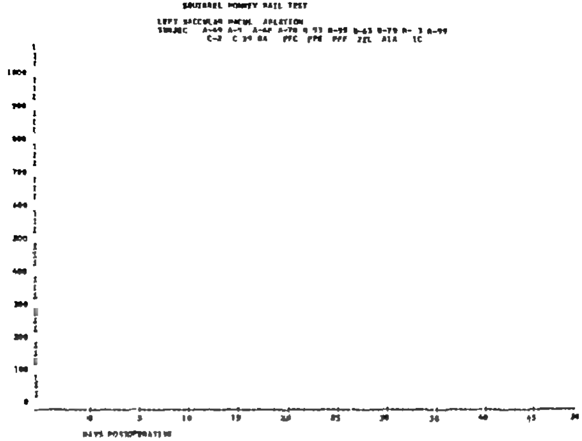

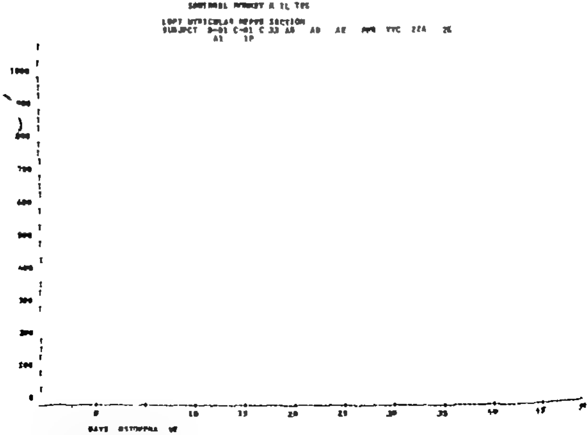

Fig 5 (A B) Computer printout scatter-graphs demonstrate different status of rail thresholds after unilateral saccular macula ablation (19 subjects) in *5 A* and after unilateral utricular nerve section (12 subjects) in *5 B*

ular nerve was found to be about 50% sectioned. In all other cases, a large section of the nerve was made and the subsequent histological investigation (Figs. 2 *A*, *B* and 3) showed that total or more than 75% of the utricular nerve had been sectioned. The longest compensation time was 28 days, and in that particular animal, the performance profile status was regained almost at the same time, that is, 30 days after the surgery. There was no simultaneous morphological alteration of any other part of the pars superior, such as the lateral semicircular canal crista which is most closely located to the utricular macula. However, there was a mild collapse of the membranous labyrinth in 2 animals. Intentional single pick insertion in utricular nerve was made in two other cases (not included in eight nerve section cases) which also exhibited severe threshold decline immediately postoperatively, but the recovery was much faster than in the animals with nerve section.

The direction of dysequilibrium after selective unilateral utricular nerve section was found to be more dominant toward the operated side. This tendency was clear in 5 (Fig. 4) and moderate in 3 cases. An oscillatory direction change was noticed in some of the post-labyrinthectomy cases along the postoperative time course, but was not found in the present series.

DISCUSSION

The degree (severity) of dysequilibrium immediately after utricular nerve section was found to be very severe and almost identical to that of post-labyrinthectomy. This is probably due to the limitation of the present dysequilibrium measurement procedure. However, the speed of equilibrium compensation was found to be different as more than two months were usually required to regain the preoperative balancing status after unilateral labyrinthectomy. The shortest compensation period in the present series was found when the utricular nerve section was about 50%; therefore, the degree of utricular nerve section may relate to the speed of functional compensation rather than to the severity of dysequilibrium when the present testing procedure is used for measurement.

It is well known that the status of bodily equilibrium after any sort of vestibular end organ lesion dynamically changes because of the compensatory activity from remaining cues of the body equilibrium system. A single (one time) postoperative test provides only limited information. Therefore, it is very important to perform the testing repeatedly after ablation, since different lesions can be compensated for over different time periods.

When comparing the present data to that of the post-saccular ablation experiment (Igarashi, 1968, 1970), it is quite evident that the macula utriculi has a much more important role in the maintenance of bodily equilibrium as measured by the squirrel monkey rail test than the macula sacculi does (Figs. 5 *A*, *B*). The reason for this difference is not known; however, the studies of Brodal et al. (1962), Brodal (1969), Stein & Carpenter (1967) and Gacek (1969) have demonstrated that the neuroanatomical topo-distribution from these two otolith end organs is to different areas of the vestibular nuclei. Probably utricular inputs have a more dominant contribution to the bodily posture and locomotion system through lateral vestibulo-spinal tract. In addition, the ecological validity of macula utriculi must be considered. Also, the different otolith end organ reaction (or behavior) against different disease entities such as congenital anomaly, viral infection, presbycusis, ototoxicity, etc., should be considered.

The different extent of utricular nerve section resulted in different lengths of time before functional compensation was completed. Even only one insertion of a fine pick into the utricular nerve area created severe dysequilibrium. This indicates that the utricular nerve and macula are extremely sensitive against even a minute mechanical or surgical trauma. On the other hand, complete unilateral section

of utricular nerve was compensated for completely without exception by all other existing equilibrium cues, in the present experiment.

The postoperative locomotive directionality toward the operated side might be due to the reduction of neural discharges which project dominantly through the ipsilateral lateral vestibulo-spinal tract. The present surgical procedure did not produce any irritative effect on utricular nerve itself or to other surrounding end organs.

ZUSAMMENFASSUNG

Nach einseitiger utrikularer Nervensektion, wurde der Zustand des Gleichgewichtsausgleiches (Grad des labilem Gleichgewichtes, Richtung der Stürze, usw) in Totenkopfaffen untersucht. Schwere Gleichgewichtsstörungen wurden nach diesem Verfahren ohne Ausnahmen beobachtet. Drei bis vier Wochen nach der Operation war jedoch das Gleichgewicht wieder vollkommen hergestellt. Der Unterschied zwischen der Gleichgewichtsfunktion nach einseitiger utrikularer Nervensektion und der Macula sacculi-Zerstörung im Totenkopfaffen wurde klar dargestellt.

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A CONTRIBUTION TO THE MECHANISM OF VESTIBULAR NYSTAGMUS

The Role of Afferent Impulses

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(Received May 27 1971)

Abstract Lateral ampullary nerve and lateral ampulla were electrically stimulated with a single shock and repetitive shocks in anesthetized and unanesthetized cats with potentials in the vestibular and oculomotor nuclei were observed. The following results were obtained.

1 Evoked potentials recorded in the vestibular and oculomotor nuclei in response to the repetitive shocks differed remarkably from the potentials produced by a single shock. A characteristic negative wave, termed an M wave, was evoked concomitant with the slow phase of nystagmus only by repetitive shocks. With the administration of muscle relaxant the nystagmus and the M waves disappeared at the same time.

2. The possibility of afferent connections from the sensory endings in the extraocular muscles to the midbrain and the brain stem, was seriously considered.

3 It was reasonably interpreted that the accumulation of M waves in the central nervous system was an important factor which also was coordinated through the neural regulation of the CNS to change the slow phase of nystagmus to the quick phase.

It has now been well established and accepted, from the investigations of a number of investigators that physiological stimulation (linear or angular accelerations) and artificial stimulation (caloric or electric stimulations) of the receptors of the labyrinth produce certain ocular deviations which are characteristic of the labyrinthine receptors so stimulated (Brodal et al., 1962).

The ocular deviations, if the subjects are above a certain level of awakeness, are interrupted periodically by quick eye movements directed toward the opposite side The neurophysiological mechanism of the periodic inter ruption of these ocular deviations has long interested neurophysiologists as well as otologists.

On the basis of clinical observations and experimental results the neural mechanism of the periodic interruption has been attributed to neural regulation in the central nervous system, especially the midbrain (Bárány 1907), the vestibular nuclei of the brainstem (Spiegel, 1929) and the brainstem reticular formation (Lorente De Nó 1928 1933). The results previously reported by one of us give support to the theory in part (Hosomi, 1964).

As a result, an opposing hypothesis based on experiments which were thought to show the excitation of the proprioceptors included in the extraocular muscles played a greater part in this mechanism appears to have been in error However the existence of the sensory endings in the extraocular muscles was demonstrated morphologically (Cooper et al. 1955) and electrophysiologically (Cooper & Daniel, 1949 1957 Cooper et al., 1951 Fillenz, 1955 Bach-y-Rita et al. 1963).

It may be that a re-evaluation together with the results of the experiments reported here, may provide a certain additional information

about the neural mechanism of the vestibular nystagmus. In these present experiments, evoked potentials produced by stimulating the lateral ampullary nerve or the ampulla with a single shock and repetitive shocks (100 c/s) were recorded and analysed in the vestibular nucleus (Nucleus medialis) and the oculomotor nucleus, and its neighbourhood, under both anesthetized and unanesthetized conditions (high spinal transection). Stimulation of the lateral ampulla with repetitive shocks elicited horizontal nystagmus, the initial eye deviation toward the non-stimulated side and returning eye movement toward the stimulated side.

Nystagmus and the evoked potentials obtained at the points above mentioned were recorded simultaneously and a characteristic wave synchronous with the slow phase of the nystagmus was observed.

METHODS

In these present experiments anesthetized and unanesthetized adult cats were used for the following procedures.

Experiments performed with anesthetized subjects

(Nembutal, Abbott) was in- (30 mg/kg, i.p.) and a tracheal cannula inserted. The tympanic bulla was opened on the left side ventrally and the vestibulum was approached. The lateral ampullary nerve was exposed for stimulation by the method of Szentagothai (1950) and Anderson & Gernandt (1954). A silver bipolar electrode (100 μ in diameter) was placed around this nerve and fixed in place with dental cement. Then the animal was decerebrated at the precollicular level. The occipital bone was removed, but the cerebellum was preserved intact. An electric square pulse stimulation ranging from 3–5 V was delivered through the isolated unit. The evoked potentials were recorded using a needle electrode of about 20 μ in diameter insulated except for the tip.

Experiments performed with unanesthetized subjects

A tracheal cannula was rapidly inserte through the tracheostoma after the inhalatio of Fluothane. A transection of the spinal cor was performed at the level of C_1 and th respiration was maintained by an artificia respirator. The tympanic cavity was opene on the left side by retro-auricular incisio Malleus and incus were removed and th stapes was carefully kept intact.

The facial nerve was cut off at its horizonta portion and then the lateral bony semicircula canal was drilled with a dental burr to mak a tiny hole.

Next the silver bipolar electrode was in serted toward the ampulla and fixed by denta cement to the bony wall of the labyrinth. Precollicular transection was performed and the cerebellum was reserved intact as same a in the procedures with anesthetized subjects. The left lateral ampulla was stimulated by repetitive shocks (0.2 msec, 100 c/s) about 2 hours after cessation of Fluothane inhalation and horizontal nystagmus towards the left side was observed. The electric stimuli and recording techniques were the same as with anesthetized subjects. Repetitive shocks (0.2 msec, 100 c/s) to the ampullary nerve or ampulla were used for observation of the ocular deviation and the nystagmus.

RESULTS

I. *Observations on Ocular Movement and Nystagmus*

In the anesthetized cat, repetitive stimulation delivered to the lateral ampullary nerve caused horizontal ocular deviation directed toward the non stimulated side. The ocular deviation began to occur one or two seconds after repetitive stimulation and the total duration until the ocular movement became fixed at a steady state, was 10 to 15 sec. After the eyes were at a steady state, no movement occurred during prolonged stimulation, such as 5 to 10 min of continual stimulation. If the repeti-

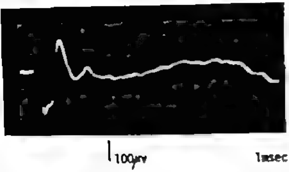

Fig 1 Evoked potential in vestibular nucleus (Nucleus medialis) in response to lateral ampullary nerve single shock stimulation. Negativity of the microelectrode is upward in this and all other records. (Nembutal anesthetized cat.)

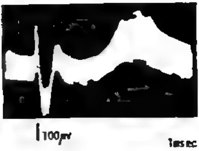

Fig 2 Superimposed evoked potentials in response to lateral ampullary nerve repetitive shocks recorded at the same point shown in Fig. 1 The characteristic negative waves ("M wave") were recorded at 5.5 msec of latency (Nembutal anesthetized cat.)

tive stimulation ceased, the eyes returned gradually to the original point. In the unanesthetized cat, repetitive stimulation to the lateral ampulla elicited horizontal nystagmus directed toward the stimulated side 2 or 3 sec after stimulation.

II. Relationship Between Ocular Movement or Nystagmus and Evoked Potentials

1 *Observation in the vestibular nucleus*

(*a*) *Observation under anesthetized conditions.* The action potential of the vestibular nucleus (Nucleus medialis) in response to a single shock to the ipsilateral lateral ampullary nerve consisted of three components, first a positive deflection followed by two negative waves as shown in Fig. 1 The latencies of each of the waves were 0.65 msec, 1.2 msec, and 2.4 msec, respectively

On the other hand, by means of the repetitive shocks which were delivered to the lateral ampullary nerve, an ocular deviation was elicited as described in the preceding section and at the same time a characteristic negative wave was recorded with a latency of 5.5 msec,

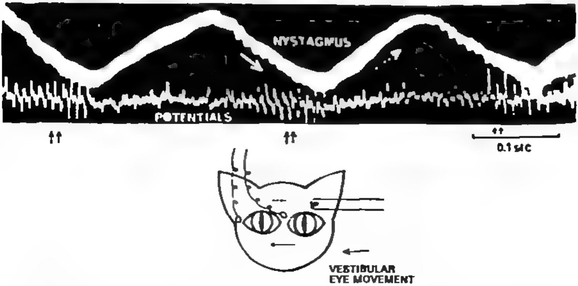

Fig 3 Nystagmus and evoked potentials were recorded simultaneously in the vestibular nucleus. M waves (arrowed ↑↑ lower trace, see Discussion) were obtained simultaneously concomitant with the slow phase (↘) of nystagmus The quick component is indicated with the arrow ( ) (High spinal cat.)

about the neural mechanism of the vestibular nystagmus. In these present experiments, evoked potentials produced by stimulating the lateral ampullary nerve or the ampulla with a single shock and repetitive shocks (100 c/s) were recorded and analysed in the vestibular nucleus (Nucleus medialis) and the oculomotor nucleus, and its neighbourhood, under both anesthetized and unanesthetized conditions (high spinal transection) Stimulation of the lateral ampulla with repetitive shocks elicited horizontal nystagmus, the initial eye deviation toward the non-stimulated side and returning eye movement toward the stimulated side.

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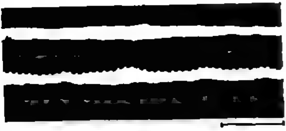

Fig 7 Intravenous administration of muscle relaxant. Nystagmus and M wave as shown in Fig. 6 were not seen in this records. (High spinal cat.) Eye movement: upper trace action potentials: lower trace.

1 6 msec and 3 0 msec respectively (Fig. 5 1-*a*, left column). Figs. 5 (1-*b*) 2 and 3 show the field potentials recorded in the vicinity of the electrode tip as shown in Figs. 5 1-*a*. The characteristic negative wave (termed an M_o wave) was evoked by the ampullary nerve repetitive shocks as shown in Fig. 5 right column. The latency of the M_o wave was about 5.5 msec. The M_o wave was recorded, accompanying the ocular movement, as observed in the vestibular nucleus. Transition of the M_o wave was observed depending on the location of the electrode tip as shown by the delayed latency and the reversal of the wave (Figs. 5-2, and 3 right column).

(*b*) *Observation under unanesthetized conditions.* A nystagmus directed toward the stimulated side was elicited by repetitive shocks under unanesthetized conditions (Fig. 6, upper tracing). Simultaneous recordings of the oculomotor evoked potentials in response to repetitive shocks showed the appearance of the M_o wave simultaneously with the slow phase of the nystagmus as observed in the vestibular nucleus (Fig. 6, lower tracing). When a muscle relaxant was administered intravenously to inhibit the extraocular muscle contraction, both the nystagmus and the M_o wave disappeared (Fig. 7).

DISCUSSION

The originating area or center for the quick phase of nystagmus has been suggested by many investigators to lie in the midbrain (Bárány 1907) vestibular nuclei (Spiegel 1929), or the reticular formation, especially the brain stem reticular formation (Lorente De Nó, 1928, 1933).

However no conclusion was reached as to the specific location for this center or area. In fact the existence of a specific area for the production of the quick component of nystagmus has not been accepted by some authors (Brodal et al., 1962, McCabe 1965) On the other hand, the eye centering system (Bender & Shanzer 1964) is well accepted as a method of understanding the mechanism of nystagmus.

The great difference in the potentials between the anesthetized and unanesthetized subject consisted in the appearance of the M_v and the M_o wave which could not be seen during the quick phase in the unanesthetized cat. The arrows (↑↑) in Figs. 3 and 6 indicate the M and the M_o wave, whose latencies are the same as those of the M and the M_o wave of the anesthetized and it is clearly shown that these waves wax and wane in accordance with the slow phase and the quick phase during the nystagmus. These waves almost entirely disappear during the quick phase, while the initial potential complex remains and there is only a diminishing of the spike height. Moreover both the M_v and M_o wave and the nystagmus disappeared following the injection of muscle relaxant.

It can be definitely considered that the M_v wave obtained in the vestibular nucleus (Fig. 2) was evoked by the same mechanism as was the M_o wave in the oculomotor nucleus (Fig 5) based on their similar mode of the appearance during eye deviation and nystagmus. According to the fact just mentioned, we use the term "M wave" instead of the M_v and the M_o wave. The M waves were recorded only in the region of the vestibular nucleus and oculomotor nucleus, and its neighbourhood independently and could not be recorded in the other area of the brain stem and midbrain.

In these present experiments, potenti

evoked by stimulating the lateral ampullary nerve or lateral ampulla with a single shock and repetitive shocks of high frequency (100 c/s) were recorded and analysed in the vestibular nucleus and the oculomotor nucleus and its neighbourhood. The evoked potential obtained in the vestibular nucleus by a single shock of the lateral ampullary nerve was composed of three components, as already described, and this potential complex had a similar pattern to the potential evoked in the vestibular nucleus by the stimulation of the utriculoampullary nerve (Shimazu & Precht, 1965 Precht & Shimazu, 1965). The potentials evoked in the oculomotor nucleus by stimulating the lateral ampullary nerve or lateral ampulla were of the same pattern as those evoked by stimulating the anterior ampullary nerve (Amatsu 1966)

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ZUSAMMENFASSUNG

elektrischen Reizungen wurden an N ampullaris 'is oder Ampulla lateralis gegeben und die Po- Vestibularis- und Okulomotorkernen wurden 'riert. Die dabei entstandenen Augenbewegungen in Bezug auf die Potentiale analysiert. Die Ergebnisse waren folgende:

1 Die Aktionspotentiale in Vestibularis- und *Okulomotorkernen waren sehr verschieden je nach* Reizungsfrequenz, d. h. der einfachen (1 mal/Sek.) oder wiederholten (100 mal/Sek.). An der anästhesierten Katze wurde ein negatives Aktionspotential, „M wave nur durch die wiederholten Reizungen registriert und Augendeviation nach der gereizten Seite wurde gleichzeitig beobachtet. Im Wachzustand wurde die Augenbewegung wie der Nystagmus durch die genannte Reizung erfolgt. Die „M wave wurde dabei nur während der langsamen Phase des Nystagmus registriert. Das Potential (M wave) und der Nystagmus erloschen völlig durch die Anwendung des Flaxedils.

2. Dann wurde eine afferente Verbindung der sensorischen Apparate in Augenmuskeln mit genannten Kernen oder Formatio reticularis sehr wahrscheinlich angedeutet.

3 Es wurde auch geschlossen, daß die Anhaufung der afferenten Erregungen in Mittelhirn und Hirnstamm an den Phasenwechsel — von einer langsamen zur einer schnellen — eine große Rolle spielen muß.

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PATHOLOGICAL AND FUNCTIONAL ALTERATIONS IN THE VESTIBULAR LABYRINTH FOLLOWING CRYOSURGERY[1]

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(Received July 16, 1971)

Abstract Definite pathologic changes were noted within the horizontal crista ampullaris after cryosurgery The amount of damage was dependent upon the temperature of the crista during cooling. For example, when the horizontal crista was cooled to −70°C (intralabyrinthine temperature +18°C) exudate was observed in the endolymphatic space. Electron microscopically however definite cellular damage (myelin figures) was detected primarily in the specialized cells (dark and light). Ruptures of the membranous wall of the crista was observed at cryosurgical dosage of −90°C (intralabyrinthine temperature +13°C). Gross histological damage was noted when the horizontal crista was cooled to −120 and −190°C (intralabyrinthine temperature +5 and −6C° respectively). The functional (rotatory tests), ultrastructural and histologic results correlate extremely well. These results indicate that the critical cryosurgical threshold dosage necessary to alter the morphology and function of the semicircular canal system is approximately −70°C (intralabyrinthine temperature +18°C).

The effects of cryosurgery upon the reactivity of the labyrinth has been investigated in our laboratory using a variety of animals (Cutt et al. 1965 1968 Wolfson et al., 1966) In our early research, the effects of low temperature surgery upon the labyrinth was evaluated by using cochlear microphonics, histologic sections, caloric tests (Cutt et al., 1965) and automated behavioral conditioning techniques (Ishiyama et al., 1971) Laboratory animals have been found to be unresponsive to caloric stimulation following cryosurgery However, examination of the temporal bones of these animals has shown that morphological alteration was restricted to the place of contact of the cryosurgical probe on the horizontal semicircular canal. These changes appeared in the form of fibrosis and bony obliteration in the perilymphatic space. Similar pathologic changes, however were commonly seen in the squirrel monkey's semicircular canal after experimental fenestration procedure (Shambaugh, 1954 1959).

Since the cryosurgical technique has been clinically successful in eliminating vertigo and nystagmus, it seems unlikely that fibrosis or new bone formation in the lateral canal could render all semicircular canals non functional. The present study was therefore undertaken to re-evaluate and assess the effects of low temperature surgery upon the vestibular end organ. The membranous labyrinth, metabolically active non-sensory cells and sensory epithelia and their neural components were carefully studied functionally by the use of rotation tests and temperature measurements and morphologically using light and electron microscopy

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MATERIAL AND METHODS

Pigeons (*Columba domestica*) ranging in weight from 300 to 350 g were used in this study because their vestibular structures can be easily exposed and processed in vivo with little or no tissue distortion. Previous studies (Ishiyama et al., 1970, 1971) have thoroughly familiarized the authors with the normal morphology of the pigeon's vestibular system.

Unilateral labyrinthectomy

The animal was anesthetized with ether and the mastoid opened in order to expose the entire horizontal semicircular canal. Exposure of the pigeon labyrinth is technically easy because it lies close to the surface of the skull and is enclosed in a network of delicate air cells which can be dissected away with curettes and picks. Under ×25 magnification the three cristae were destroyed.

Labyrinthine tests and recording of nystagmus

Rotatory tests for examination of the labyrinthine function were performed pre- and post-operatively using a slight modification of Aschan's (et al.) technique (1955). Labyrinthectomized pigeons were positioned on the rotating table with the head directly above the axis of rotation. A photocell was placed directly under the pigeon's bill, the output of the photocell was amplified and recorded by a Beckman Dynograph. Using this technique it was possible to record the pigeon's head nystagmus (Fig. 1). The rotation device was accelerated at a rate of 12 /sec^2 to constant velocity of 120 /sec (20 r.p.m.) after 2 min and decelerated at the rate of 12 /sec^2.

Cryosurgery

A Linde Cryosurgery Unit (Type CE 3 No. 371771, Union Carbide) was used. The surgical tip ■ 1.6 mm in diameter. A special coaxial copper thermocouple is soldered in place at the tip of the probe and measures the probe tip's temperature within the range of ±6 C. The probe tip can be controlled at any temperature between +40 to −195 C.

The sites of cryosurgical probe application were as follows: (*A*) on the bony crus of the horizontal semicircular canal (approximate position of the probe is illustrated in the inset Fig. 2 *A*), (*B*) on the endosteum of the crus, (*C*) in the perilymphatic space of the crus, and (*D*) on the bony crista ampullaris. The various probe temperature used were −30, −40, −70, −120 and −190 C.

Temperature measurements

After exposure of the horizontal semicircular canal, a small hole was made with a 4–0 burr in the mid-portion of the crista ampullaris, a copper constantan thermocouple (0.25 mm o.d.) mounted on a micrometer drive was positioned at the edges of the opening made in the horizontal crista ampullaris and inserted at any desired point. The thermocouple output was amplified using range card of +70 to −70 C (Leeds & Northrup, Philadelphia). Temperature measurements were then performed during the cryosurgical applications (detailed technique for temperature measurements, see Ishiyama & Keels, 1970).

Histology

The animals were sacrificed by mean of intravital cardiac perfusion using Heidenhains-Susa solution 3 weeks after cryosurgery. The specimens were then decalcified using Decal, dehydrated and embedded in celloidin and sectioned at 20 μ intervals. The sections were stained with hematoxylin and eosin and mounted on glass slides.

Electron microscopy

The pigeons were anesthetized with ether and the semicircular canal exposed. The bone was dissected away from the lateral side of the semicircular canal and its ampulla. Glutaraldehyde (5% glutaraldehyde in 0.1 M phosphate buffer pH 7.3) was then introduced directly into the membranous ... The

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PATHOLOGICAL AND FUNCTIONAL ALTERATIONS IN THE VESTIBULAR LABYRINTH FOLLOWING CRYOSURGERY[1]

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(Received July 16 1971)

Abstract Definite pathologic changes were noted within the horizontal crista ampullaris after cryosurgery The amount of damage was dependent upon the temperature of the crista during cooling. For example, when the horizontal crista was cooled to −70°C (intralabyrinthine temperature +18°C) exudate was observed in the endolymphatic space. Electron microscopically however definite cellular damage (myelin figures) was detected primarily in the specialized cells (dark and light). Ruptures of the membranous wall of the crista was observed at cryosurgical dosage of −90°C (intralabyrinthine temperature +13°C). Gross histological damage was noted when the horizontal crista was cooled to −120 and −190°C (intralabyrinthine temperature +5 and −6C° respectively). The functional (rotatory tests) ultrastructural and histologic results correlate ex ly well. These results indicate that the critical surgical threshold dosage necessary to alter the ology and function of the semicircular canal m approximately −70°C (intralabyrinthine mperature +18°C).

The effects of cryosurgery upon the reactivity of the labyrinth has been investigated in our laboratory using a variety of animals (Cutt et al. 1965 1968 Wolfson et al., 1966) In our early research, the effects of low temperature surgery upon the labyrinth was evaluated by using cochlear microphonics, histologic sections, caloric tests (Cutt et al., 1965) and automated behavioral conditioning techniques (Ishiyama et al., 1971) Laboratory animals have been found to be unresponsive to caloric stimulation following cryosurgery However, examination of the temporal bones of these animals has shown that morphological alteration was restricted to the place of contact of the cryosurgical probe on the horizontal semicircular canal. These changes appeared in the form of fibrosis and bony obliteration in the perilymphatic space. Similar pathology changes, however were commonly seen in the squirrel monkey's semicircular canal after experimental fenestration procedure (Simbaugh, 1954 1959)

Since the cryosurgical technique has been clinically successful in eliminating vertigo and nystagmus, it seems unlikely that fibrosis and new bone formation in the lateral canal could render all semicircular canals non-functional. The present study was therefore undertaken to re-evaluate and assess the effects of low temperature surgery upon the vestibular end organ. The membranous labyrinth metabolically active non-sensory cells and sensory epithelia and their neural components were carefully studied functionally by the use of rotatory tests and temperature measurements and morphologically using light and electron microscopy

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MATERIAL AND METHODS

Pigeons (*Columba domestica*) ranging in weight from 300 to 350 g were used in this study because their vestibular structures can be easily exposed and processed in vivo with little or no tissue distortion. Previous studies (Ishiyama et al., 1970, 1971) have thoroughly familiarized the authors with the normal morphology of the pigeon's vestibular system.

Unilateral labyrinthectomy

The animal was anesthetized with ether and the mastoid opened in order to expose the entire horizontal semicircular canal. Exposure of the pigeon labyrinth is technically easy because it lies close to the surface of the skull and is enclosed in a network of delicate air cells which can be dissected away with curettes and picks. Under ×25 magnification the three cristae were destroyed.

Labyrinthine tests and recording of nystagmus

Rotatory tests for examination of the labyrinthine function were performed pre- and postoperatively using a slight modification of Aschan's (et al.) technique (1955). Labyrinthectomized pigeons were positioned on the rotating table with the head directly above the axis of rotation. A photocell was placed directly under the pigeon's bill, the output of the photocell was amplified and recorded by a Beckman Dynograph. Using this technique it was possible to record the pigeon's head nystagmus (Fig. 1). The rotation device was accelerated at a rate of 12 /sec² to constant velocity of 120 /sec (20 r.p.m.) after 2 min and decelerated at the rate of 12 /sec².

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A Linde Cryosurgery Unit (Type CE 3 No. 371771 Union Carbide) was used. The surgical tip is 1.6 mm in diameter. A special coaxial copper thermocouple is soldered in place at the tip of the probe and measures the probe tip's temperature within the range of ±6 C. The probe tip can be controlled at any temperature between +40 to −195 C.

The sites of cryosurgical probe application were as follows. (*A*) on the bony crus of the horizontal semicircular canal (approximate position of the probe is illustrated in the inset Fig. 2 *A*) (*B*) on the endosteum of the crus, (*C*) in the perilymphatic space of the crus, and (*D*) on the bony crista ampullaris. The various probe temperature used were −30, −40, −70, −120 and −190 C.

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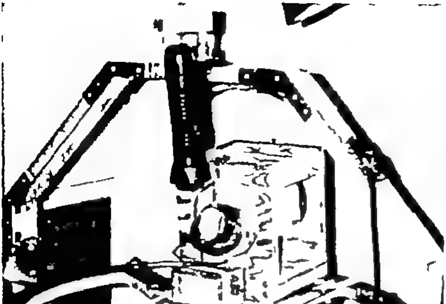


Fig 1 Photograph illustrating a rotating apparatus. A headholder (shown by an arrow in inset) demonstrated easy recording of pigeon's head movement onto photocell (shown by white arrow)

pigeon was then decapitated, and the membranous ampulla dissected out and placed in fresh cold glutaraldehyde solution for 2 hours. The specimens were post fixed in Palade fixative (1952) for 2 hours, dehydrated with alcohol and propylene oxide and embedded in Epon using Luft's technique (1961) Sections were then cut with Sorvall Porter Blum MT 2 ultramicrotome The sections were stained with uranyl acetate (Watson, 1958) and lead hydroxide (Karnovsky 1961) and studied with a Jeolco JEM 7 electron microscope at 80 k

RESULTS

Temperature measurements

Temperature measurements were performed to determine the temperature of the horizontal crista ampullaris during cryosurgery using a variety of probe application procedures. Th

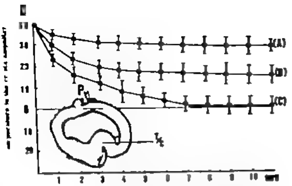
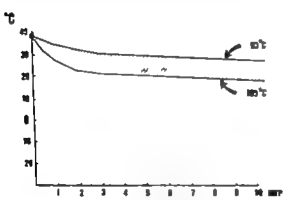


Fig. 2 A. The curves summarized the actual temperature changes (*T/C*) which occurred within the horizontal crista ampullaris when the crus (*P*) was cooled locally to −90°C for 11 min. The following sites of cryo-probe application were used. (*A*) on the bony crus, (*B*) on the endosteum of the crus, and (*C*) in the perilymphatic space of the crus. Each point on the curve is the a erage of three tests.



F g. 2 B. The curve illustrating actual temperature changes which occurred within the crista ampullaris when the cryo-probe was maintained at a temperature of −90 and −190°C for 10 min on the bony crus.

curves in Fig. 2 *A* summarize the actual temperature changes which occurred within the horizontal crista ampullaris when the crus of the horizontal canal was cooled locally with probe tip temperature of *−90 C for 11 min* (the position of the crus is illustrated in Fig. 2 *A*). This temperature was previously found to be necessary for the reduction or elimination of labyrinthine function. The following sites of probe applications were used: (*A*) on the bony crus, (*B*) on the endosteum of the crus, and (*C*) in perilymphatic space of the crus of the horizontal semicircular canal. These results clearly demonstrated that heat conductivity through the bony canal to the crista ampullaris was very poor (distance between crista ampullaris and the site of probe application of the crus was approximately 6 mm).

When the cryo-probe was maintained on the bony crus at the temperature of −190 C which is near the coolest temperature of liquid nitrogen, and −90 C for each 10 min the actual temperature in the crista ampullaris was +18 and +27 C respectively (Fig. 2 *B*).

The endosteum exposure allowed better heat conductivity than the bony crus application, however fibrous and new bone formation in the perilymphatic space of the horizontal canal regularly followed this technique.

The above observation made it possible to perform cryosurgical procedures upon the bony crista ampullaris and produce intralabyrinthine temperatures equal to the temperature which had eliminated semicircular canal function in earlier studies. This was accomplished by adjusting the temperature of the cryosurgical probe to produce the desired temperature in the crista ampullaris. It was

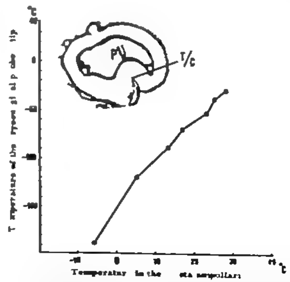


Fig. 3. The curve illustrating the relationship between the actual temperature in the crista and the temperature of the cryo-surgical probe on the bony crista ampullaris. Inset photograph demonstrates approximate position of cryo-probe (*P*) and thermocouple (*T C*) in the crista ampullaris.

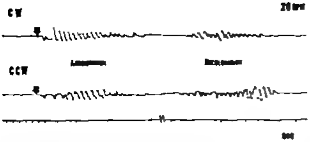


Fig 4 Normal rotatory reaction was recorded from clockwise and counterclockwise rotation during acceleration and deceleration of 12°/sec²

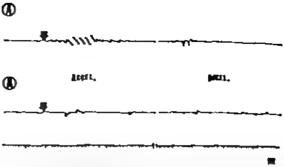


Fig. 5. Nystagmographs recorded 3 weeks after cryosurgery (*A*) Illustrates marked reduction of head nystagmus after cryosurgery with −70°C for 9 min. No response was recorded (*B*) after exposure to −120°C for 9 min.

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Fig. 3 demonstrates the relationship between the temperature in the crista and the temperature of the cryosurgical probe on the bony crista ampullaris. The graph served as a nomogram for the production of desired temperature changes.

Functional significances

Rotatory tests performed on the experimental animals were illustrated in Figs. 4 and 5 Control rotatory test results showed 1.5 to 2.0 sec of latency and about 15 to 16 sec of head nystagmus from acceleration and deceleration (12/sec²) respectively After unilateral labyrinthectomy the animal s head tilted to the operated side and demonstrated the spontaneous head nystagmus to the normal ear (so-called paralytic nystagmus) This spontaneous head nystagmus was gradually diminished within a few days of the operation. Cryosurgery was then performed on the other ear 3 weeks after the first unilateral labyrinthectomy Spontaneous head nystagmus again resulted but the direction was toward the first operation ear (compensation nystagmus). Re-

Table I *Summary of the histology following cryosurgery on the horizontal crista*

Animal	Cryosurgery °C	Cryosurgery minutes	Sensory cells	Specialized cells	Cupula	Exudate in endolymph	Rupture of membrane	Other vest. organs
A	−30	9	Normal	Normal	Normal	(−)	(−)	Normal
B	−40	9	Normal	Normal	Normal	(±)	(−)	Normal
C	40	9	Normal	Normal	Normal	(±)	(−)	Normal
D	−70	9	Normal	Normal	Shrink	(+)	(−)	Normal
E	−70	9	Normal	Normal	Shrink	(++)	(−)	Normal
F	−90	9	Partial degeneration	Partial degeneration	Partial detachment	(++)	(−)	Normal
G	90	9	Partial degeneration	Partial degeneration	Partial detachment	(++)	(−)	Normal
H	90	9	Partial degeneration	Partial degeneration	Complete detachment	(++)	(+)	Normal
I	−90	9	Partial degeneration	Partial degeneration	Partial detachment	(++)	(−)	Normal
J	−120	9	Severe degeneration	Severe degeneration	Disappear	(++)	(+)	Normal
K	−120	9	Severe degeneration	Severe degeneration	Disappear	(+++)	(+)	Normal
L	−190	9	Severe degeneration	Severe degeneration	Disappear	(+++)	(+)	Normal

Fig. 6. Photomicrographs of the horizontal crista ampullaris of pigeons treated with (*A*) −30°C, (*B*) −70°C and (*C*) −190°C for 9 min. These pigeons were sacrificed on the 21st postoperative day. Note that no damage was detected from −30°C animal *A*. The cell damage was not clearly demonstrated from −70°C animal *E* though presence of exudate in the endolymphatic space was obvious (shown by arrow in *B*). Severe cell damage of the sensory and specialized epithelia was obvious from −190°C animal *L* (shown by arrow in *C*).

tatory tests were repeated 3 weeks after the cryosurgery. Normal rotatory reaction was observed after the horizontal crista was cooled to −30 and −40 C for 9 min (intralabyrinthine temperature +28 and +25 C respectively). The animals exposed to −70 and −90 C for 9 min (intralabyrinthine temperature +18 and +13 C respectively), however demonstrated marked reduction in rotatory reaction 3 weeks after the cryosurgery. Rotatory responses were abolished in those animals which were exposed −120 and −190 C for 9 min (Fig. 5 *A*, *B*).

Histology

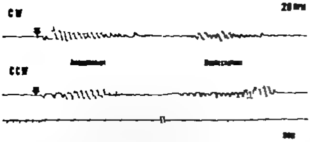
Temporal bone sections from 12 pigeons have been examined by light microscopy after undergoing cryosurgery on the bony crista ampullaris. Emphasis was placed upon the membranous labyrinth, sensory epithelia, specialized cells (dark and light) and the neural components of the horizontal and vertical canal crista, utricle saccule and cochlea. The results are summarized in Table I.

Pathological changes are discussed for each of following categories of cryosurgical dosage and horizontal crista ampullaris temperatures: (1) probe temperature −30 and −40 C = intralabyrinthine temperature +28 and +25 C respectively, (2) probe temperature −70 C = intralabyrinthine temperature +18 C, (3) probe temperature −90 C = intralabyrinthine temperature +13 C, and (4) probe temperature −120 and −190 C = intralabyrinthine temperature +5 and −6 C respectively.

Pigeon exposed to −30 and −40°C for 9 min failed to show any structural changes in the horizontal crista and surrounding area (Fig. 6 *A*).

Pigeons exposed to −70 C (intralabyrinthine temperature +18 C) on the other hand, exhibited pathological changes in the endolymphatic space evidenced by the presence of exudate and shrinkage of the cupula (Fig. 6 *B*). The sensory epithelia and specialized cells appeared to be within normal limits by light microscopic observations.

When the horizontal crista ampull



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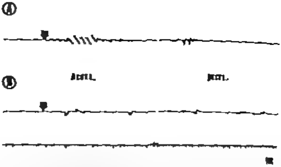

Fig 5. Nystagmographs recorded 3 weeks after cryosurgery (*A*) Illustrates marked reduction of head nystagmus after cryosurgery with −70°C for 9 sec. No response was recorded (*B*) after exposure to −120°C for 9 min.

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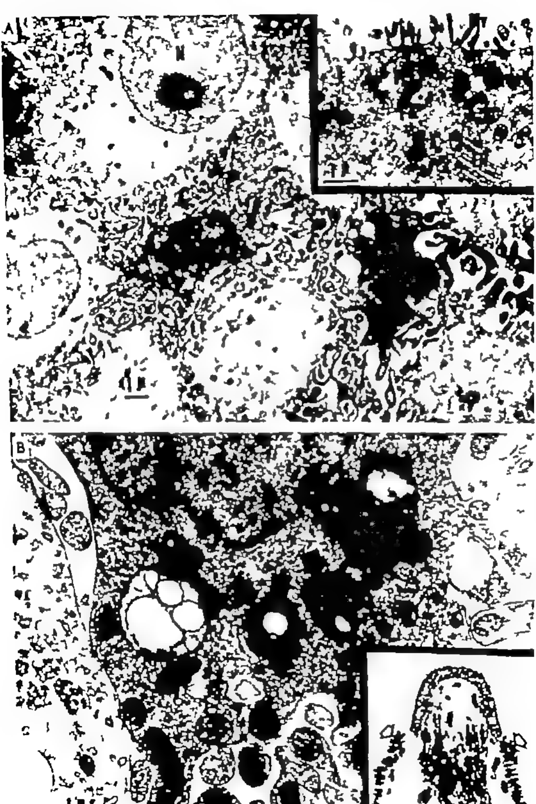
L	−190	9	Severe degeneration	Severe degeneration	Disappear	(+++)	(+)	Normal


A
B

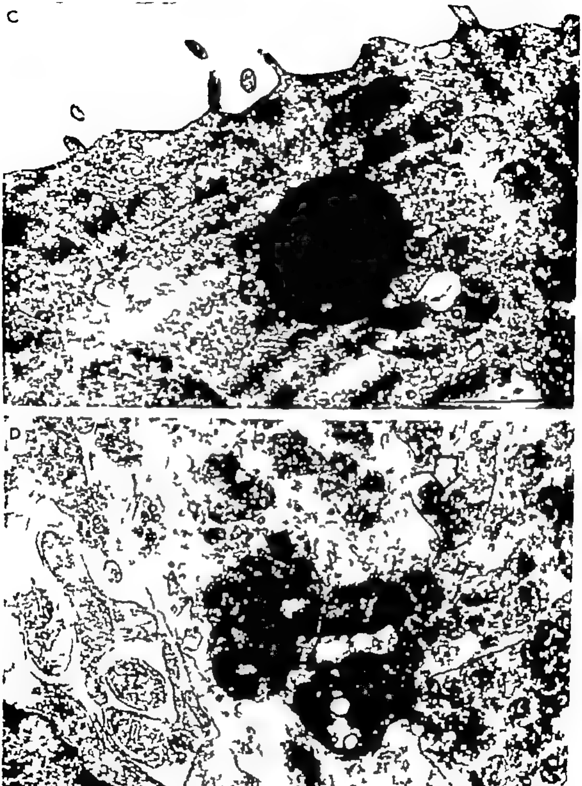

C
D

Fig. 9. Electron micrographs demonstrating hair cells of type I from horizontal crista ampullaris. The apical portion of the sensory epithelia exhibited vacuolization, though their nerve endings include nerve calyxes appeared to be normal (*A*). The supporting cells (*B*) demonstrating extensive vacuolization in the apical portion of the cells. This animal was exposed to −70°C for 9 min.

There was no fibrosis or new bone formation in the crista ampullaris of any specimen.

Electron microscopic observations

To further investigate the effects of cryosurgery upon the labyrinth, the ultrastructure of the horizontal crista ampullaris was also investigated in 13 pigeons using direct cooling on the bony crista ampullaris.

These pigeons were sacrificed and prepared for electron microscopic examination 3 weeks after cryosurgery.

The animals exposed to −30 C (intralaby

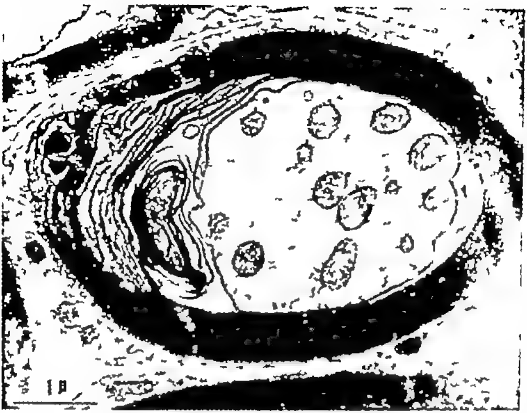


Fig 10 Electron micrograph demonstrating a portion of myelin sheath from horizontal crista ampullaris. Most of the myelinated fibres appeared to be disorganized and the mitochondria are enlarged. This animal was exposed to −90°C for 9 min.

rinthine temperature +28 C) exhibited normal cytoarchitecture of the dark and light cells (Fig. 8 *A*) and the sensory epithelia.

Normal histology except for the appear ,e of exudate, was observed in animals ose horizontal crista ampullaris was cooled to −70 C (intralabyrinthine temperature +18 C) however very interesting ultrastructural changes were noted in the dark (osmiophilic) and light (osmophobic) cells and sensory epithelia. Degeneration was more pronounced in the dark and light cells than in the sensory epithelia and neural components. The severity of these patologic changes varied from cell to cell, but were present to some degree in most cells.

The electron micrographs in Fig. 8 *B* *C* and *D* illustrates the pathologic changes which occurred in the dark and light cells of a crista which had been cooled to 70 C (intralabyrinthine temperature +18 C) In the dark cells (Fig. 8 *B*) lipofuscin granules, which often tend to have myelin figures, were observed throughout the cytoplasm which contains normal mitochondria. These myelin figures resemble in structure the myelin sheath of nerves. The luminal surface of the dark cells, in their normal state, are usually made-up of a large number of microvilli (Fig. 8 *A*). A marked reduction of these microvilli was noted after cryosurgery (Figs. 8 *C* 12). In the supranuclear region of the dark cells single membrane limited inclusion bodies were often observed containing osmiophilic debris (Fig. 10). The light cells exhibited the presence of lipofuscin granules often showing the appearance of myelin figures and lysosomes (shown by arrows in Fig 8 *D*). A cluster of homogenous granules also appeared in the cytoplasm. The apical portion of the sensory epithelia showed a slight swelling and extensive vacuolization in the cytoplasm (Fig 9) Transverse section

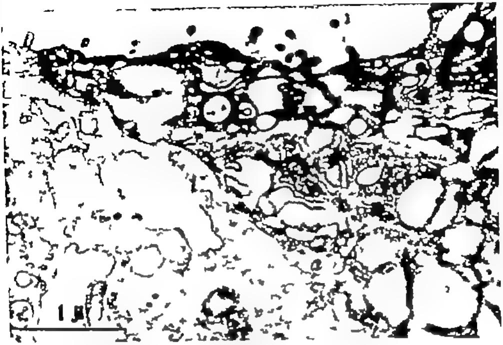


Fig. 11. Electron micrograph demonstrating a portion of dark and light cell after exposure to −120°C for 9 min. The confluences between the vacuoles are obvious.

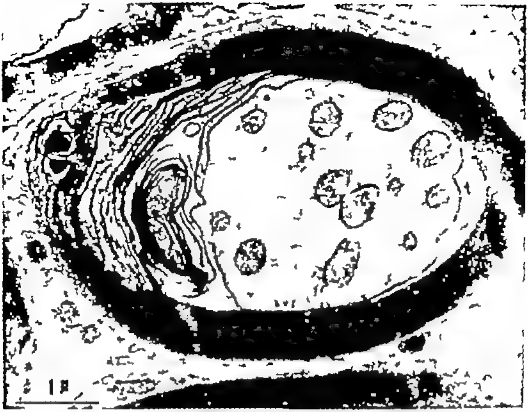
of myelinated axons were normal in appearance

The ultrastructure of the crista ampullaris which had been cooled to −90 C (intralabyrinthine temperature +13 C) showed basically the same pathological changes as the cristae which were cooled to −70 C with the exception that more cells were affected. At this "cryo-dosage" the myelinated axons appeared to be disorganized and the mitochondria were slightly enlarged (Fig. 10)

Gross pathological changes were observed in the horizontal crista which were cooled to −120 and −190 C (intralabyrinthine temperature +5 and −6 C respectively). Distinct cell degeneration was observed in the dark and light cells, sensory epithelia and myelinated nerves. The most impressive feature of degeneration in the dark and light cells was the enormous number of vacuoles which frequently contained flocculent material. Confluences between the vacuoles was observed (Fig. 11). The sensory epithelia exhibited vacuolization in the supranuclear region (Fig. 12)

DISCUSSION

In a previous report (Cutt et al., 1968) concerning the histology of the vestibular labyrinth following endosteum cryosurgery it was stated that the only pathological condition common to all animals after cryosurgery was the presence of fibrosis or new bone formation within the perilymphatic space at the site of probe application. However it was very difficult to evaluate true cryo-effects using this procedure. Shambaugh (1954 1959) for example, demonstrated histologically the results of a fenestration operation using the squirrel monkey He stated that connective tissue and new bone formation was confined to the periosteal layer of the capsule 10 days after the fenestration operation. He also reported that obliteration of the perilymphatic space due to fibrosis and osteogenesis



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Noticeable changes were observed primarily in the specialized cells (dark and light) and to a small degree in the sensory epithelia when the crista was cooled to −90 C (intralabyrinthine temperature +13 C). Probe temperature of −120 C (intralabyrinthine temperature +5 C) and lower created severe cellular damage and rupture of the membranous wall, thus suggesting the intermixture of fluids between the endolymph and perilymph. Following rupture, contamination of the endolymph by perilymph might alter the chemical composition of the labyrinthine fluids sufficiently to interfere with neural exitation. In addition, this rupturing may reduce endolymphatic pressure.

House (1968) performed cryosurgery on the promontory. He wanted to create a shunt between the otic and perotic labyrinth. He speculated from his clinical cases that the equalization of fluid pressure between endolymph and perilymph might be important for relieving the symptom of vertigo in patients with Ménière's disease.

Endolymphatic shunt (Austin & Hart, 1965; Austin, 1968; Shambaugh, 1966; Shea, 1966, 1968; Pulec, 1968), subarachnoid shunt (House, 1962) and sacculotomy (Cody et al., 1967; Fick, 1968) have been used to release or equalize endolymphatic pressure. Our histological results also suggest that a rupture in the membranous wall after cryosurgery could release or equalize labyrinthine fluid pressure.

It can be also concluded from histological observation that the critical dosage for causing cell damage in the crista ampullaris was somewhere around −90 C for 9 min (intralabyrinthine temperature during the cooling was +13 C).

Electron microscopic observations of the crista ampullaris indicated that the first pathological changes occurred in the dark and light cells when the crista was cooled to −70 C (intralabyrinthine temperature +18°C). The dark and light cells showed myelin figures in the cytoplasm. These structures superficially resemble the myelin sheath of nerve tissue. The presence of myelin figures, however, suggest cellular degeneration, especially degeneration of the membranous components (Freeman, 1964). Clusters of homogenous granules commonly appeared in the light cells after the crista was cooled. These clusters appear to be an early stage of cell degeneration.

Dohlman (1965) has demonstrated physiological evidence that the dark cells remove sodium and chloride ions and water solvents through the cell against osmotic and electric gradients. He also demonstrated increased vesiculation of the light cells following injection of sodium chloride into endolymph. Since it is known that water is removed from the endolymph while sodium ions are transported across the membrane of the dark cells, a mechanism must exist which replenishes the water and maintains the proper volume of endolymph. These facts strongly suggest a hypothesis that the changes which occurred in the dark and light cells after the cryosurgery could indicate a reduced endolymph production, thus providing a possible explanation for the functional imbalance in the normal vestibular organ.

The ultrastructural changes in the sensory epithelia when cooled to −70 C (intralabyrinthine temperature +18°C) were fewer than those observed in the dark and light cells. The only changes which occurred in the sensory epithelia was increased vacuolization of the cytoplasm in the supranuclear region of the cells.

Lower dosages of cryosurgery exhibited degeneration of the dark and light cells and sensory epithelia. In addition, disorganization of the myelinated fibres and enlarged mitochondria were detected.

Cutt (1968) presented a hypothesis that damage in the mitochondria is the first sign of the cell degeneration after cryosurgery. This hypothesis must be eliminated because after cryosurgery the dark and light cells and the sensory epithelia exhibited well preserved crista mitochondrialis while myelin figures were apparent in the cytoplasm. Therefore, it is safe to state that the first sign of patho-

logical alteration after cryosurgery is not interference with mitochondrial function but more likely interference with local cell function characterized anatomically by myelin figures in the cytoplasm of the specialized cells. The appearance of myelin figures does not imply inevitable cell death because this change is localized, at first, in a small area of the cytoplasm and the cell may survive. However the appearance of myelin figures throughout a cell is a sign of cell death (Freeman, 1964)

The data compiled in this study presents firm foundations and logical explanation for observed clinical results following cryosurgical procedures to the labyrinth. Clinically it has been found that the nystagmus response to caloric stimulation after cryosurgery was eliminated or markedly reduced in most cases, and that 36% of successful cases demonstrated little or no change in the postoperative caloric test. These alterations may be explained hypothetically by the observation of myelin figures in the cells.

Stahle (1957) and Sjöberg et al (1963) have demonstrated that rotatory tests were satisfactory stimuli for the evaluation of head nystagmus responses in pigeons. Using modifications of their technique, a definite correlation was observed between pathology and function of the horizontal crista ampullaris following cryosurgery. Normal semicircular canal function was observed after the horizontal crista was cooled to −30 and −40 C (intralabyrinthine temperature +28 and +25 C). Animals whose crista were cooled to −70 and −90 C (intralabyrinthine temperature +18 and +13 C respectively) however demonstrated marked reduction in head nystagmus 3 weeks after the cryosurgery. No vestibular response was recorded in pigeons in which the horizontal crista was cooled to −120 and −190 C (intralabyrinthine temperature +5 and −6 C respectively)

These results correlate well with histological and electron microscopic observations, and it appears that the critical threshold dosage necessary to alter the morphology and function of the semicircular canal system is approximately −70 C for [illegible] min (intralabyrinthine temperature +18 C)

These experimental data also demonstrated conclusively that the cryosurgery upon the bony crista ampullaris gave rise to no effects in the cochlea and saccule

Preliminary temperature measurements were performed on 2 patients with Ménière's disease prior to performing a total labyrinthectomy. The cryosurgical probe was positioned on the blue line of the horizontal semicircular canal at the temperature of −160 C. The temperature of the horizontal crista ampullaris in both patients ranged from +17 to +20 C. These intralabyrinthine temperature measurements correlate well with the experimental data. The temperature correlation between the patients with Ménière's disease and the experimental data in this study strongly supports the findings from this study as the explanation for the clinical results following cryosurgery of the labyrinth

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ZUSAMMENFASSUNG

In der horizontalen Kristae ampullaris wurden deutliche histologische Veränderungen nach Kältechirurgie beobachtet. Das Ausmaß der Veränderung war von der Temperatur der Kristae während der Kühlung abhängig. Zum Beispiel, wenn die horizontale Krista auf +18°C (Kälteproben Temperatur −70°C) gekühlt wurde, konnte im endolymphatischen Raume aktivierte Materie beobachtet werden. Sehr interessante Ergebnisse wurden mit dem Elektronenmikroskop gefunden. Bei −70°C erschienen die ersten Veränderungen in den hellen und dunklen Zellen. Beide Zellenarten wiesen Myelin Figuren im Zytoplasma auf welche auf eine Degeneration der Membranstruktur hindeuten. In den hellen Zellen wurden Gruppen von homogenen Körpern beobachtet, möglicherweise eine Frühstufe der Zelldegenerierung. Im Sensoryepithelium konnte als einzige Veränderung eine Zunahme der Vacuolen im oberen Teil der Zellen beobachtet

werden. Die funktionellen, histologischen und ultrastrukturalen Befunde stimmen sehr gut miteinander überein. Diese Befunde zeigen, daß die kritische Temperatur des Intralabyrinthes ungefähr bei +18°C (Kälteproben Temperatur −70°C) liegt um die Morphologie und Funktion des semizirkularen Kanales zu ändern. Tiefere Temperaturen verursachen stärkere Gewebeschäden.

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TESTING OF THE VESTIBULAR SYSTEM BY SINUSOIDAL ANGULAR ACCELERATION

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(Received May 11 1971)

Abstract Sinusoidal stimulation of the horizontal semicircular canals was evaluated in 22 normal and 53 abnormal individuals. Nystagmic responses were analysed for both linearity and preponderance as a function of the period and specific frequency of stimulation. Many of the abnormal vestibular cases demonstrated a directional preponderance which, at low frequency stimulation, was particularly suggestive of severe pathology This examination enhanced the caloric evaluation, demonstrated possible mechanisms of compensation and provided a method of following changing pathologic conditions.

Ever since Bárány (1907) introduced the clinical usefulness of rotational tests for vestibular evaluation, there has been a great deal of terest in the development and improvement f existing acceleration techniques. The trend has been for more sophisticated methods em ploying precise stimuli and recording equipment cupulometry (van Egmond & Groen, 1953) l'épreuve giratoire liminaire (Montandon, 1954) and vestibulometry (Torok, 1961)

Recently several investigators (Niven et al., 1965 Cramer et al., 1963 and Eviatar & Goodhill, 1968) described methods for establishing a continuous harmonic or sinusoidal oscillation. Such techniques provided an efficient and quantitative acceleration stimulus with simple methods of evaluating the nystagm response. Although the stimulus was initial restricted to laboratory animals and norm subjects, preliminary reports suggested application to the clinical evaluation of pa tients.

In an attempt to analyse the potentia diagnostic value of the sinusoidal stimulus, was the purpose of the present study to deter *mine the characteristic parameters of the nys* tagmic response both in normal and abnormal individuals. The data derived from these deter minations were then applied to a variety of clinical problems, comparing results from sinusoidal stimulation to those of other vestibular tests. It was anticipated that this stud would clarify some of the difficulties i rotational testing, as well as provide method to distinguish vestibular pathology

METHODS

Equipment

A yaw axis device, consisting of an en capsulated chair and torque motor (Inland Motors Corporation) generated the sinusoid angular acceleration stimulus. The system wa driven directly by the motor and provided n clues of motion from vibration, noise, or backlash. The stimulus waveform was devel oped by a low output sine wave generato and controlled by a decade voltage divider

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Symmetry and speed were monitored by a servo-system employing a high precision tachometer. In routine use, the chair could be varied from 0 to 50 r.p.m. over a frequency range of 0.02 Hz to 0.24 Hz, provided that the required peak acceleration did not exceed 0.6 rad/sec^2.

Recording equipment for nystagmus consisted of large Beckman silver electrodes affixed to the center of the forehead and the outer canthi of the eyes. The signals were amplified with a Grass low-level d.c. preamplifier in a Grass Model 7 recorder. The low-frequency time constant was modified to 2.4 sec and the high-frequency response set at 35 Hz ($^1/_2$ amplitude on the Grass recorder). Separate channels were employed to describe the time intervals, acceleration, raw and differentiated signals.

Electronystagmographic data were processed through differentiating and clamping circuits which provided a signal roughly proportional to the velocity of eye movement or eye deviation. The calibration was obtained by having the subject move his eyes in a 10-degree arc between two lights. This corresponded to a pen deflection of 10 mm for raw nystagmus and 2 mm for derived nystagmus.

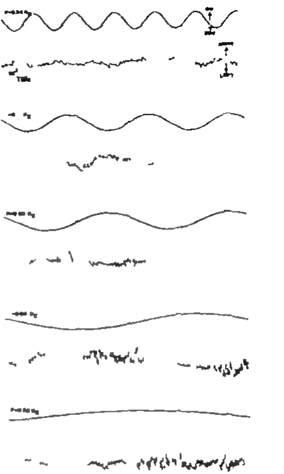

Fig. 1. Normal nystagmic responses to sinusoidal stimuli over a range of 0.24 to 0.02 Hz at 0.4 rad/sec^2.

Procedures

Individuals undergoing vestibular evaluation were instructed about the procedure of recording nystagmus during sinusoidal rotation. At the start of testing, the subject's head was inclined forward 30 degrees by a headrest to bring the lateral canals into the horizontal position. Various mental tasks were provided to maintain alertness. All recordings were obtained with the eyes open inside the darkened chamber.

After standardization of the corneoretinal potential, the stimulus was administered as an oscillation from the high to low frequency (Fig. 1). Usually the peak acceleration was maintained at 0.4 rad/sec^2 but, in separate experiments, 6 normal airmen were subjected to accelerations of 0.2, 0.4 and 0.6 rad/sec^2 respectively. The stimulation was initiated in a counterclockwise direction at a pre-determined frequency and peak acceleration for at least four complete cycles. Two-minute intervals separated tests to provide for the recalibration of eye movement and to allow for the postrotatory decay of nystagmus.

For the analysis of normal response, subjects previously evaluated by history, physical, audiogram, bithermal caloric, positional and optokinetic tests (Mathog & Cramer 1971) were administered the sinusoidal stimulus. Two normal groups were established: one, consisting of 10 pilots and 6 airmen, and another 6 airmen. In the larger group ($N = 16$) the test was given at 0.4 rad/sec^2 from 0.24 to 0.02 Hz,

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Table I The peak velocity of nystagmus in response to sinusoidal stimuli (N = 16)

Stimulus parameters					
Frequency (Hz)	0.24	0.12	0.08	0.04	0 02
Period (sec)	4.2	8.3	12.5	25.0	50 0
Peak velocity (r.p.m.)	2.6	5 4	8.0	16.0	32 0
Peak acceleration (rad/sec²)	0.4	0.4	0.4	0 4	0.4
Peak velocity of nystagmus					
Average (deg/sec)	9 6	20.9	40.9	78 8	130.3
Range of values (deg/sec)	15.5–14.1	10.6–32.0	23 4–64 4	42 0–132.0	83.0–155.0
S.D. (deg/sec)	2.6	6.5	11.9	23 4	21.0

normal response at values greater than 20%. In between values for sinusoidal and caloric stimulations were classified as borderline responses.

RESULTS

Stimulus–response characteristics in normal subjects

(1). *Frequency and period of acceleration.* Upon analysis of the sinusoidal stimulation data, it became apparent that one of the most important variables of the stimulus was the duration of acceleration. The stimulus duration was determined by the period of the sine wave, but also could be expressed by the reciprocal function of frequency. Any adjustment to lower the frequency or lengthen the period while holding the peak acceleration constant, produced an increase in the velocity of nystagmus.

The effects of changing frequencies and corresponding period from 0.24 to 0 02 Hz were evaluated at 0.4 rad/sec² (Table I and Fig. 1). At the higher frequency of stimulation the duration of acceleration was so short that the response was barely perceptible. In fact, the nystagmic velocity approached a threshold which was difficult to determine against a background of non-nystagmic eye oscillation. Upon lengthening the period, however, nystagmus became more prominent. Throughout the range of 0.24 to 0.02 Hz the velocity of the slow component of nystagmus increased in a linear fashion. Only at 0 02 Hz was there an indication of non-linearity in the system. This was demonstrated by a progressively smaller increment in the eye velocity in response to the lower frequencies.

(2). *Peak acceleration.* Although the effectiveness of stimulation could be evaluated in terms of duration, there still was a need to define another important characteristic of the

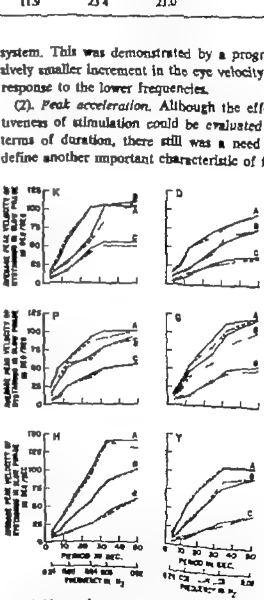

Fig. 3 Nystagmic responses of 6 normal subjects as a function of peak acceleration and cyclic periods or frequency. Plots of *A*, *B* and *C* [illegible], respectively, accelerations of 0.6, 0.4, and [illegible] rad/sec² — [illegible] beating nystagmus, right-beating nystagmus

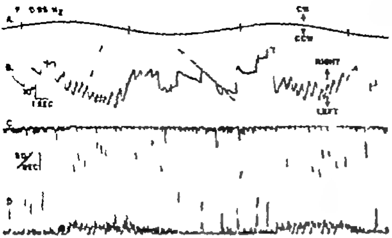

Fig 2 En example of method of analysis of the nystagmic response for an individual with a left cerebellopontine angle tumor Line *A* represents the recording of the accelerometer and demonstrates the frequency direction and magnitude of oscillation. Line *B* shows the slope method of determining the maximum slow-phase velocity of nystagmus while lines *C* and *D* define the clamped derivatives in two directions.

while in the smaller group ($N=6$) different peak accelerations were employed over a similar frequency range.

In the study of the abnormal vestibular system patients referred by the Wilford Hall USAF Medical Center the USAF School of Aerospace Medicine, and Randolph Air Force Base were considered for evaluation. On the basis of a history of vestibular disease and in most cases, abnormal bithermal caloric tests, 53 individuals were selected for stimulation at 0 4 rad/sec² Although in many patients a diagnosis could not be established (9), there were a significant number with ...ière s disease (13) and partial or complete surgical labyrinthectomy (6) Other diagnoses included vestibular neuronitis (10) labyrinthine concussion (3), vascular insufficiency (3) and cerebellopontine angle tumor (1).

Analytical

Recordings of nystagmic responses were performed for five test frequencies of sinusoidal acceleration (Fig. 1) Each frequency was analysed for at least four cycles and, in some cases up to ten cycles, to exclude initial transient phenomena due to the starting of the apparatus.

The velocity of eye movement during the slow component of nystagmus was measured by a slope determination and clamped derivative, both demonstrated in Fig. 2. Maximum velocity of nystagmus was calculated for each cycle over at least two cycles, and then averaged for those beats which were orientated in one direction When symmetry was perfect the peak velocity of nystagmus was averaged for all cycles, disregarding the direction of the beats.

Directional preponderance within the system was determined by the difference in average peak velocity of nystagmus in opposite directions. This was calculated according to the formula. $[(V_L - V_R)/(V_L + V_R)] \times 100\%$ where V_L or V_R represented the maximum velocity of the slow component of nystagmus averaged in the left or right direction (Mathog & Cramer 1971) Average peak velocity was ... determined by an average of slopes or measurement of a clamped derivative. Theoretically perfect symmetry corresponded to 0% while complete asymmetry was expressed as ±100%

In order to compare the sinusoidal determinations with caloric data, arbitrary standards were established. Using the Jongkees & Philipszoon (1963) formulae of paresis or preponderance and their description of variability a normal caloric response was set at values less than 15% while an abnormal response was assigned values greater than 25% Subsequent evaluation of preponderance from sinusoidal stimulation suggested the designation of a normal response at less than 10% and an ab...

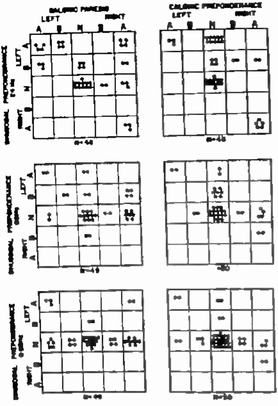

Fig. 4. A frequency distribution comparing the degree and direction of abnormality from caloric and sinusoidal stimulations. All patients were not included in every category. Normal (*N*), borderline (*B*), and abnormal (*A*) responses are defined in the text.

(2). *Midfrequency stimulation.* In contrast to the peculiar unidirectional response at high frequency the analysis of responses at midfrequency (0.08 Hz) demonstrated a nystagmic preponderance similar in direction to the preponderance induced by caloric stimulation (Fig. 4). If a patient had a tendency for nystagmus to one side on caloric testing, this same direction persisted upon evaluation of the sinusoidal response. It appeared that testing at 0.08 Hz measured a phenomenon similar to that determined by the caloric evaluation, thereby confirming previous test results.

(3). *Low-frequency stimulation.* On the other hand, an increase in stimulus intensity developed at low-frequency stimulation provided new and important information about vestibular pathology. At 0.02 Hz, regardless of the results from previous caloric tests or even from higher frequencies of harmonic stimulation, almost all patients became border line or normal (Fig. 4). Only a few retained abnormal status. In fact, where there were 20 to 22 abnormal cases at 0.24 Hz, there were only 8 cases at 0.02 Hz. This change in category would not have been significant, except that all 8 cases demonstrated severe pathology.

Low-frequency stimulation was probably the most effective sinusoidal stimulus, since it appeared to separate patients with more active vestibular disease from those with lesser problems. The pathologic condition of those 8 patients, in contrast to the entire group was characterized by recent vestibular symptoms and partial or complete destruction of the labyrinth. Diagnoses included surgical labyrinthectomy (3) trauma with unilateral vestibular and auditory damage (2), Menière's disease (1) and cerebellopontine angle tumor (1). Although one patient was suspected of having a temporal lobe tumor this diagnosis was never established.

DISCUSSION

Evaluation of the vestibular system in normal subjects with sinusoidal angular accelerations produced several types of nystagmic responses, possibly reflecting different measures of vestibular sensitivity. When high- middle or low frequency stimulations were analysed as separate conditions, it was possible to demonstrate normal, threshold, linear or nonlinear nystagmic responses corresponding to periods of acceleration. At high frequency (0.24 Hz) an acceleration of 0.4 rad/sec^2 barely evoked a response, while at midfrequency (0.08 Hz) the nystagmus was directly related to the period. Only at lower frequency (0.02 Hz) did the response become less than proportional to the change in stimulus. All cases, regardless of intensity of stimulation, demonstrated a tendency toward symmetry.

These characteristics of the normal response

provided standards for comparing the abnormal responses in the vestibular system. Although one could have evaluated such parameters as a lag or lead in response as proposed by Niven et al. (1965), or distortion in amplitude of nystagmus, it should be noted that analysis was directed toward the symmetry or preponderance of nystagmic velocity This appeared as one of the easily determined, less variable measures of the system. Furthermore *data also could be correlated with caloric* determinations.

Evaluation of symmetry in the abnormal group of subjects revealed different patterns developing with changes in stimulus frequency The analysis demonstrated. (1) distortion at high frequency from stimulus artifact (2) directional preponderance similar to the results of caloric tests at midfrequency and (3) what appeared as a separation of severe from lesser pathology at the lower frequency of stimulation. Although the pattern of response for each individual throughout an entire frequency range of 0.24 to 0.02 Hz was useful, the clinical application was most valuable at the greater stimulation (0.02 Hz) employing the longer period of lower frequency

In addition to these general relationships of stimulus and response other information derived from individual cases demonstrated the possibility of evaluating a changing pathology Usually the directional preponderance elicited by sinusoidal stimulation remained constant for at least 24 hours, but in some patients, evaluation at a later time demonstrated a change in direction and a tendency toward symmetry The phenomenon was particularly characteristic of those few patients where there was recovery following injury to the vestibular system i.e. head injury and destructive labyrinthectomy The observation was not unique, since Igarashi (1970) had noted similar recovery patterns in the squirrel monkey following ablation of parts in the vestibular end organ

On the basis of such information changes in the symmetry of response were used to determine the extent of healing processes. If the directional preponderance remained constant over a period of time, it was possible to assume a lack of compensation and the likelihood of an active or progressive lesion. Such was the case in the patient with an acoustic tumor since preponderance remained unchanged for 14 months, and then became less marked with removal of the lesion.

In conclusion sinusoidal stimulation, as *defined at a specific frequency and peak acceleration*, proved useful in the evaluation of the vestibular system. When applied to abnormal cases, it was possible to determine the directional preponderance of the individual and distinguish severe types of pathology Although the technique could not determine the particular pathologic ear it did provide a potential method for following a changing disease state In conjunction with caloric tests the sinusoidal stimulus allowed a more complete understanding of the vestibular system.

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ZUSAMMENFASSUNG

Eine wellenförmige Reizung der horizontalen Bogengänge wurde bei [illegible] gesunden und 53 kranken Personen durchgeführt. Der hierdurch entstehende Nystagmus wurde auf Gleichförmigkeit und richtungsgebundenes Überwiegen, sowie auf den Zusammenhang von Dauer und spezifischen Frequenzbereichen untersucht. Bei erkranktem Vestibularapparat zeigt sich vielfach ein richtungsgebundenes Überwiegen des Nystagmus. Dies läßt besonders bei niedrigfrequenter Reizung krankhafte Veränderungen vermuten. Die Untersuchung ergänzt die kalorische Auswertung und auf mögliche Ausgleichsmechanismen hin und bietet sich als eine Methode an, um Krankheitsprozesse zu überwachen.

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provided standards for comparing the abnormal responses in the vestibular system. Although one could have evaluated such parameters as a lag or lead in response as proposed by Niven et al. (1965) or distortion in amplitude of nystagmus, it should be noted that analysis was directed toward the symmetry or preponderance of nystagmic velocity This appeared as one of the easily determined, less variable measures of the system Furthermore, *data also could* be correlated with caloric determinations.

Evaluation of symmetry in the abnormal group of subjects revealed different patterns developing with changes in stimulus frequency The analysis demonstrated (1) distortion at high frequency from stimulus artifact (2) directional preponderance similar to the results of caloric tests at midfrequency and (3) what appeared as a seperation of severe from lesser pathology at the lower frequency of stimulation Although the pattern of response for each individual throughout an entire frequency range of 0.24 to 0 02 Hz was useful, the clinical application was most valuable at the greater stimulation (0 02 Hz) employing the longer period of lower frequency

In addition to these general relationships of stimulus and response, other information derived from individual cases demonstrated he possibility of evaluating a changing pathogy Usually the directional preponderance elicited by sinusoidal stimulation remained constant for at least 24 hours, but *in some patients*, evaluation at a later time demonstrated a change in direction and a tendency toward symmetry The phenomenon was particularly characteristic of those few patients where there was recovery following injury to the vestibular system i.e head injury and destructive labyrinthectomy The observation was not unique, since Igarashi (1970) had noted similar recovery patterns in the squirrel monkey following ablation of parts in the vestibular end organ.

On the basis of such information changes in the symmetry of response were used to determine the extent of healing processes. If the directional preponderance remained constant over a period of time, it was possible to assume a lack of compensation and the likelihood of an active or progressive lesion. Such was the case in the patient with an acoustic tumor since preponderance remained unchanged for 14 months, and then became less marked with removal of the lesion.

In conclusion, sinusoidal stimulation, as defined at a specific frequency and peak acceleration proved useful in the evaluation of the vestibular system. When applied to abnormal cases, it was possible to determine the directional preponderance of the individual and distinguish severe types of pathology Although the technique could not determine the particular pathologic ear it did provide a potential method for following a changing disease state. In conjunction with caloric tests the sinusoidal stimulus allowed a more complete understanding of the vestibular system.

ACKNOWLEDGMENT

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ZUSAMMENFASSUNG

Eine wellenförmige Reizung der horizontalen Bogengänge wurde bei 22 gesunden und 53 kranken Personen durchgeführt. Der hierdurch entstehende Nystagmus wurde auf Gleichförmigkeit und richtungsgebundenes Überwiegen, sowie auf den Zusammenhang von Dauer und spezifischen Frequenzbereich untersucht. Bei erkranktem Vestibularapparat zeigt sich vielfach ein richtungsgebundenes Überwiegen des Nystagmus. Dies läßt besonders bei niedrigfrequenter Reizung krankhafte Veränderungen vermuten. Die Untersuchung ergänzt die kalorische Auswertung und weist auf mögliche Ausgleichsmechanismen hin und bietet sich als eine Methode an, um Krankheitsprozesse zu überwachen.

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bined with Brown's tube oscillograph for observations and recordings.

II *Observations in clinical cases with loss of labyrinthine excitability*

These subjects consisted of 9 cases with the bilateral loss of labyrinthine responses and 3 cases with a unilateral loss of labyrinthine responses. Labyrinthine responses were evaluated as absent in cases with a failure of response to caloric stimulation (ice water 20 ml). The evaluation of bilateral loss of excitability of the labyrinths was confirmed by a complete absence of response to rotatory stimulation (10 rot. for 20 sec). There was bilateral loss of labyrinthine response in 2 cases of labyrinthitis, 2 cases of streptomycin intoxication, 3 cases of acute peripheral vestibular palsy and 2 cases of sudden deafness with vestibular disturbance. The labyrinthine response was found to be lost unilaterally in 1 case of direct labyrinthine injury and 2 cases of acute peripheral vestibular palsy. These cases were subjected to the following tests. (However, all tests could not be carried out in all cases of our series, so that the number of cases listed in Results differs for each test. Emphasis was placed in the present study on cases of bilateral loss of labyrinthine responses.)

1. Investigation was carried out on clinical cases on the recovery curve for the H waves in evoked electromyograms appearing in the gastrocnemius muscle under electrical stimulation of the posterior tibial nerve. This test was designed by Magladery (1955) for testing of the spinal reflexes in man. The H reflex is a proprioceptive reflex of the gastrocnemius muscle conducted by the posterior tibial nerve through the spinal monosynaptic reflex arc. Observations on the H-reflex in cases of loss of labyrinthine function provide a clue as to whether the labyrinth has an inhibitory influence or a facilitatory one on proprioceptive reflexes. The recovery curve was plotted according to the method of Magladery: a double shock was given by [illegible] short waves. Surface electrodes were used for the leading of the EMG from the [illegible] muscle. Measurements were made of the amplitude of the H-wave (H_1) in response to [illegible] shock (conditioning shock) and that (H_2) [illegible] second shock (test shock), to calculate the ratio H_2/H_1 expressed in percentage [illegible]. The interval between shocks was [illegible] vary from 30 msec to 1000 msec, to make a recovery curve by plotting values [illegible] shock interval on the ordinate and [illegible] H_2/H_1 on the abscissa.

2. The following tests were carried out [illegible] order to elucidate the characteristics of [illegible] ataxia, i.e. body sway in the upright [illegible] in cases with loss of labyrinthine response.

(*a*) Observations were made on [illegible] movements of the head and the center of [illegible] ity in the upright position. [illegible] was performed in the following [illegible] subject was instructed to put [illegible] The helmet was connected with [illegible] meter fixed to the ceiling, which [illegible] head deviation to the anterior [illegible] as well as right and left [illegible] movements detected with the [illegible] was recorded on an X-Y [illegible] graph with load cells under [illegible] of a quadrangular plank [illegible] sides was used for [illegible] the center of gravity [illegible] and posterior as well [illegible] tions of the center of [illegible] with two pairs of load [illegible] opposite corners of the [illegible] was required to stand [illegible] together on the center [illegible] sagittal surface fitted [illegible] Sway at the center of [illegible] 2 pairs of load cells [illegible] recorder. The registration [illegible] 60 sec with both [illegible] respectively.

(*b*) Polygraphic [illegible] was carried out [illegible] analysis of the sway [illegible]

Fig 1 A crab with removed otocysts.

the nature of the sway in cases with loss of labyrinthine response Correlation analysis permits the determination of the average time course in the sway For polygraphic registration of body sway a 10-channel polygraph was used to record eye movements (horizontal and vertical), sway of the head (displacement and acceleration) sway at the center of gravity and electromyograms (anterior tibial m. and gastrocnemius m) in a simultaneous manner Electronystagmography was used for registration of eye movements, and the above-noted cephalography for registration of head sway (displacement) For registration of head sway (acceleration) 2 accelerometers were installed on a helmet for cephalography Simultaneous with polygraphy of body sway sway of the head (displacement) and the center of gravity was recorded on a 4 channel data recorder to permit correlation analysis using a medical computer The conditions for the analysis were address number 256 address time 200 μsec, and total delay 131072 msec, that is, the time axis of correlogram was as wide as about 13 sec.

RESULTS

A *Study of the posture of animals with destroyed labyrinths*

1 *Posture of crabs with bilaterally removed otocysts.* The posture of crabs with removed otocysts is shown in Fig 1 The legs are seen extended with the body erected vertically These animals sometimes tumble backward while walking This may be interpreted as representing a posture necessitated by decreased antigravity tonus of the legs.

2. *Posture of bilaterally labyrinthectomized rabbits.* The posture of bilaterally labyrinthectomized rabbits is shown in Fig 2. The head is retroflexed and the forelegs are extended. Such a posture persisted postoperatively for more than 3 months.

EMG was performed on the muscles of the nape and forelegs in order to determine whether such a posture is due to relaxed muscular tonus as stated by Ewald's theory or conversely to increased muscular tonus. The results are shown in Fig 3. The upper

Fig 2 A rabbit with the labyrinths bilaterally destroyed.

part of the figure illustrates EMGs taken preoperatively and the lower part, after bilateral labyrinthectomy The electrical discharge was increased postoperatively in the muscles, especially the extensor muscles of the nape and forelegs: there was elevated tonus of the antigravity muscles following labyrinthectomy

Thus, the change in the posture of rabbits with destroyed labyrinths may not be explained by reduced muscular tonus, but by increased tonus of the antigravity muscles. Such enhanced tension of the antigravity muscles, in turn, seems to result from increased proprioceptive reflexes. The results of our study in this respect are discussed below

B. *Study in cases of loss of labyrinthine response*

1 *Recovery curve of H waves in evoked EMGs.* Observations were made on the recovery curve for H-waves in evoked EMGs in cases without labyrinthine function in order to determine whether or not there exists such an increase in tonus of the antigravity muscle even in humans with loss of labyrinthine function as is seen in labyrinthectomized rabbits and whether the increased muscular tonus, if present, is due to enhanced proprioceptive reflexes.

Fig. 4 shows the findings in a case of loss of bilateral labyrinthine response due to streptomycin intoxication. In this case, the recovery curve is different from that of normal subjects (the values for whom are shown by solid lines). There occurs initial facilitation i.e. the appearance of H_2 even within a short interval of only 80 msec between double shocks. The percentage of H_2/H_1 also exceeds 100% at intervals of over 130 msec: there also exists a supernormal period.

Examination of the recovery curve for the

Fig 1 A crab with re-
moved otocysts.

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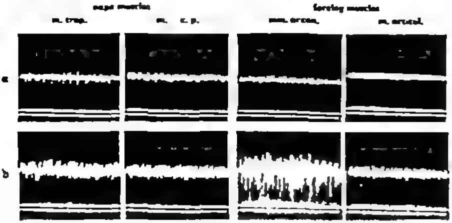

Fig 3 EMGs of the ne[illegible] and foreleg before [illegible] after bilateral labyrinthec- tomies in a rabbit (*a*) Be- fore operation, (*b*) after labyrinthectomies.

legs revealed such a supernormal period in 4 out of 5 cases with bilateral loss of laby rinthine response. And, in 2 of 3 cases of the unilateral loss of labyrinthine response a supernormal period was recognized for the leg contralateral to the side of the impaired laby rinth.

These results indicate that loss of laby rinthine response is associated with an in- crease in spinal reflexes. Such an increase in spinal reflexes, i.e. the stretch reflexes, causes an increase in extensor muscle tonus. In other words, there is an increase in antigravity mus- cular tonus due to enhanced proprioceptive re flexes in cases of bilateral loss of labyrinthine [illegible]ponse. Furthermore it was shown that [illegible]l reflexes were increased in the leg on the [illegible]-injured side in cases of unilateral laby [illegible]inthine disturbance This means that uni- laterally labyrinthectomized animals prese[illegible] an increase in extensor tonus of the contra- lateral leg and that a similar change occurs [illegible] muscular tonus in cases of unilateral loss of labyrinthine response

2. *Ataxia in cases of bilateral loss of lab- rinthine response* As stated above, spinal re- flexes were found to be increased in case[illegible] where the labyrinthine response was lo[illegible] bilaterally Such an increase in spinal reflex[illegible] constitutes a characteristic feature of lab- rinthine ataxia as follows:

(*a*) *Body sway in the upright posi[illegible]* Fig. 5 shows the sway at the center of grav[illegible] in the upright position in cases of bilat[illegible] loss of labyrinthine response due to str[illegible] mycin intoxication. Characteristically the

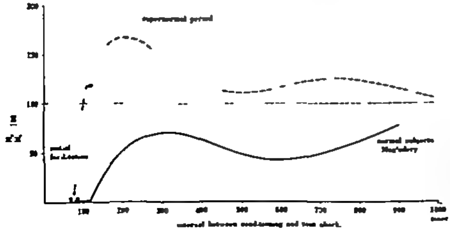

Fig 4 Recovery curve [illegible] the H-waves [illegible] EMGs [illegible] a case with [illegible] lateral loss of labyrin[illegible] response.

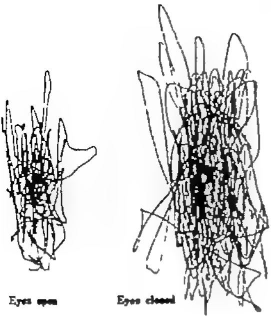

Fig. 5. Sway at the center of gravity in the upright position in a case of bilateral loss of labyrinthine response.

is seen repeated forward and backward sway with both open and closed eyes.

Table I shows a comparison of the pattern of body sway in normal subjects and in cases of loss of labyrinthine response. In normal subjects, the sway often assumes a centripetal or diffuse type, whereas forward and backward type is seen in most cases of the latter group. A centripetal or diffuse type is seen also in some cases of the latter group, especially in those with a prolonged loss of labyrinthine response. In some cases, the sway changed from a forward and backward type to a pattern combined with right and left type over a course of 2 years. The results shown in the table are concerned with the initial examination.

These results indicate that forward and backward sway in the upright position is one of the features of body sway in cases of bilateral loss of labyrinthine response. This pattern of body sway was present also in cases with injury to the brain-stem such as patients with Foville's syndrome due to vertebral artery insufficiency. We believe that such a pattern is one of the types of body sway associated with increased proprioceptive reflexes.

(b) Polygraphic registration of body sway in the upright position and correlation analysis of the sway curve. Fig. 6 shows a polygram

Table I. *Patterns of body sway in the upright position in normal subjects and in cases with bilateral loss of labyrinthine response*

Condition	Pattern of sway: Centripetal type	Diffuse type	Multicentric type	Forward and backward type	Right and left type
Normal subjects (31 cases)					
Sway of head					
Eyes open	12	9	4	6	0
Eyes closed	11	10	5	5	0
Sway at center of gravity					
Eyes open	11	9	5	6	0
Eyes closed	10	10	4	7	0
Cases with bilateral loss of labyrinthine reaction (5 cases)					
Sway of head					
Eyes open	0	2	0	3	0
Eyes closed	2	0	0	3	0
Sway at center of gravity					
Eyes open	1	0	0	4	0
Eyes closed	0	0	0	5	0

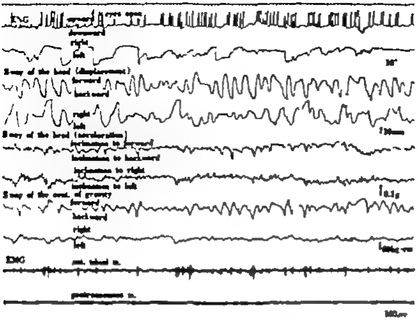

Fig 6 Polygraphic record body sway in a case of bilater loss of labyrinthine response

of body sway in a case with loss of bilateral labyrinthine response due to suppurative labyrinthitis. The polygram, as distinct from the statogram, enables a separate observation of forward and backward sway and right and left sway over the course of the time A periodicity is seen in the sway of the head and the center of gravity The amplitude is larger for forward and backward sway The findings from correlation analysis of the sway are illustrated in Fig. 7 *a* The correlograms show the average course of the sway A sine wave process, a cycle of about 0.4 Hz and a conver value of about 0.2, is seen in correlograms for forward and backward sway of the head and the center of gravity The cycle is elongated in the correlograms for swaying i the right and left direction Fig 7 *b* represen correlograms for body sway in a case wi traumatic cervical myelosis. This is a ca presenting increased patellar tendon reflex with clonus of the legs and evidently enhanc proprioceptive reflexes. The correlograms fo this case exhibit a typical pattern of bod sway associated with increased propriocept reflexes. A comparison of the correlogra for forward and backward sway in cases wi bilateral loss of labyrinthine response and th with cervical myelosis reveals a higher ext of regularity for the latter although there i a similarity between the two with respect to th period and sine wave process presented. Co

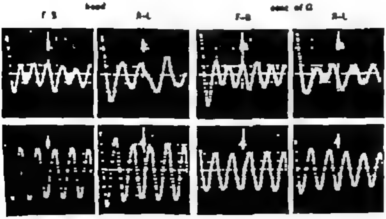

Fig 7 Correlograms of bod sway in the upright postur a case with loss of labyrinthi response and that with cervical myelopathia (*a*) A case with b lateral loss of labyrinthine re sponse, (*b*) a case with traumat cervical myelosis.

relation analysis of body sway demonstrated a correlogram with the same features in 3 of 5 cases with bilateral loss of labyrinthine response.

These results of correlation analysis of body sway in the upright position indicate that increased proprioceptive reflexes are responsible for the periodic forward and backward body sway in cases with bilateral loss of labyrinthine response, and that some of the features of labyrinthine ataxia can be attributed to increased proprioceptive reflexes.

DISCUSSION

In studies on the posture and muscular tonus in labyrinthectomized animals and on the muscular tonus and ataxia in clinical cases with loss of labyrinthine response, we found that there is increased muscular tonus due to enhanced proprioceptive reflexes in humans or animals with loss of labyrinthine response. This is a finding that contradicts the statement by Ewald (1892) Huizinga (1934) and Buddenbrock (1952) that animals subjected to labyrinthine destruction have reduced muscular tonus attributable to the loss of Ewald's Labyrinthtonus". Therefore, consideration must be given to how symptoms associated with loss of labyrinthine function may be otherwise interpreted.

What matters first is how labyrinthectomized animals posture. Ewald (1892) stated that pigeons suffering bilateral labyrinthine destruction hold their heads approximately in the median plane but strongly retroflex their heads when a cap is placed on the head so as to interrupt vision. Buddenbrock (1952) exhibited a picture showing a labyrinthectomized pigeon with the head markedly retroflexed by a weight attached to the bill. Magnus (1924) stated that labyrinthectomized cats hold their heads upright but with horizontal and vertical pendular movements and that all the cats subjected to labyrinthine destruction creep backward. The fact that these cats crept backward suggests the presence of increased extensor tonus of the forelegs. Ishikawa (1958) found that rabbits with destroyed labyrinths bend the head. However Aramaki (1969) pointed out in rabbits, and Suzuki (1969) in rabbits and pigeons, that animals assume a nose-up head position following bilateral labyrinthine destruction. Thus, most authors since Ewald except Ishikawa referred to the nose up head position of animals suffering labyrinthine destruction.

The second question is whether the change in posture associated with labyrinthine destruction is caused by decreased muscular tonus as discussed by Ewald, Buddenbrock and Huizinga or increased tonus of the antigravity muscles. Ewald and Huizinga concluded that muscular strength is reduced in pigeons with destroyed labyrinths, based on an observation of the extent of deviation of their head with a weight attached to the bill. Buddenbrock noted that the neck of the pigeon was completely relaxed following bilateral destruction of the labyrinths, exhibiting a picture of a pigeon with destroyed labyrinths, whose head is strongly retroflexed by a weight attached to the bill. Ishikawa referred to decreased electric discharges in an EMG of the neck of labyrinthectomized rabbits The result of his study however differs from that of Aramaki, Suzuki and the present authors in the observed posture of rabbits with the labyrinths destroyed bilaterally Suzuki stated that "bilateral labyrinthine lesions induced symmetrical depressed muscle tonus" pointing out the nose-up head position of a rabbit with destroyed labyrinths. Fulton & Dow (1938) stated that bilateral destruction of the labyrinth causes generalized diminution of postural contraction in monkeys presenting a thalamic pattern following complete removal of areas 4 and 6. Magnus stated, on the other hand, that loss of generalized muscular tonus could hardly be seen in cats with destroyed labyrinths. Rademaker (1935) reported that no marked diminution of extensor tonus of the legs was observed in dogs with destroyed labyrinths. Batini et al. (1957) stated that the extensor rigidity of deafferented forelegs of de

cerebrated cats persists even after bilateral section of the eighth nerve, contrary to what was reported by Stella and Teuzian and Ter zulo Thus, no agreement is available from the results thus far reported. We are of the opinion that EMG findings in rabbits with destroyed labyrinths suggest the posture of these animals as being indicative of increased tonus of the antigravity muscles.

Finally it is of interest to know why de struction of the labyrinths was followed by strain on the antigravity muscles. We found proprioceptive reflexes enhanced in cases of loss of labyrinthine function as demonstrated by the recovery curve for H waves in evoked EMGs in these cases. This finding shows that an increase in antigravity muscular tonus in humans or animals suffering loss of laby rinthine function is attributable to increased proprioceptive reflexes as a release phe nomenon resulting from labyrinthine destruc tion In a detailed study on vestibular influences on spinal reflexes, Gernandt et al. (1957) stated that "after application of high frequency stimulation to the vestibular nerve long-lasting depressant effects as tested by segmental spinal reflexes are observed" and further Gernandt (1960) described that "ex perimental evidence implicates the reticular formation as the origin of this long-lasting in [illegible]" These reports are helpful in con[illegible] the mechanism of the increase in [illegible]uscular tonus following labyrinthine destruc tion.

In the present study we elucidated some of the characteristics of labyrinthine ataxia, plac ing special emphasis on the necessity of examining the functional connection between the labyrinth and proprioceptive reflexes.

ZUSAMMENFASSUNG

Seit Ewald ist eine Erklärung für die Veränderungen in der Haltung von labyrinthzerstörten Tieren mit der Abschwächung des Muskeltonus dank des Verlustes von „Labyrinthtonus" möglich.

Indem wir die Haltung von statocysten-entfernten Krebsen und labyrinthzerstörten Kaninchen, die Wiederkehrkurve von H-Wellen im provozierten EMG-Bild an Krankenbeispielen, bei denen die beiderseitige labyrinthogene Erregbarkeit verlorengegangen war, und die Schwingungen des Körpers bei aufrechter Haltung beobachtet und ihre Korrelationsanalyse durchgeführt haben, haben wir es verständlich gemacht, daß die oben erwähnten Veränderungen in der Haltung einschließlich charakteristischer Schwingungen des Körpers, aufgrund verlorengegangener labyrinthogener Reaktionsfähigkeit, sicherlich aber auch zum Teil als Folge des verstärkten Tonus der gravitationswidrigen Muskels aufgrund einer Steigerung proprioreptiver Reflexe verursacht werden können.

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REACTIONS TO CORIOLIS STIMULATIONS AND POSTROTATORY ENG-RESPONSE

A Study on Pilot-candidates and Pilots

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Abstract. The postrotatory ENG-responses of pilot candidates showing no, moderate or strong vegetative reactions after Coriolis stimulations were compared with those of pilots flying different types of aircraft. It could be illustrated that: (*a*) the smaller a person's vegetative resistance towards rotatory stimuli, the higher his postrotatory ENG-responses and the higher the difference between right and left turns; (*b*) jet pilots during their flying training show a habituation of their vegetative reflexes and seem to develop a high sensitivity and a good balance of their vestibular system; (*c*) this development towards higher sensitivity is less pronounced in fixed-wing pilots; (*d*) this development was not found in helicopter pilots.

The vegetative reactions to Coriolis stimulations in non-flying personnel are very different from one person to another On the other hand, almost all well-trained pilots have a marked resistance to Coriolis stimulations. Pilot-candidates, prone to motion sickness at the initial examination reveal a shift towards resistance during their flight training. This improvement towards resistance is accompanied by changing nystagmographical responses to rotatory stimuli.

In 1954 Aschan, using cupulometry described such changes of the reactions of fighter pilots in comparison with non-flying subjects. He found lower values in the duration of nystagmus and in the duration of post rotatory sensation in all fighter pilots. The threshold of postrotatory sensation was found to be higher in fighter pilots than in non-aviators. Preber (1958) investigated pilots before and after their training period and found shorter nystagmus, lower slow-phase velocity and shorter turning sensation, induced by flying.

These oft-quoted findings by Aschan and Preber are contrary to the observations, occasionally mentioned by our jet-pilots, that they feel an increasing sensitivity towards rotatory stimuli during their flying-training. It was the purpose of this investigation to clarify these contradictory facts.

METHOD

In our ENT-department of the German Air Force Institute of Aviation Medicine all pilot candidates and pilots have to perform as a part of the routine examination the "Vestibular Adroitness Test" published by Lansberg in 1954 Bending the head 90 downward and back to the upright position while being rotated at a velocity of 180 /sec, all three semicircular canals are stimulated, causing a Coriolis sensation of tilting to the right. The reac

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tions to this test are classified in five categories:

Lansberg Type I Very good performance, no vegetative symptoms.

Lansberg Type II. Good performance and/or moderate vegetative symptoms.

Lansberg Type III Poor performance and considerable complaints of nausea, cold sweat and pallor

Lansberg Type IV Poor performance and serious disturbance caused by nausea

Lansberg Type V Vomiting and nausea with delayed recovery

In the present investigation we compared the electronystagmographical postrotatory reactions of pilot-candidates with the reactions of pilots.

Subgroups of the pilot-candidates

(*a*) 30 candidates belonging to category Lansberg Type I in the Vestibular Adroitness Test

(*b*) 25 candidates belonging to category Lansberg Type III.

(*c*) 30 candidates belonging to category Lansberg Type IV/V

Subgroups of the pilots

(*a*) 30 experienced jet pilots belonging to category Lansberg Type I in the Vestibular Adroitness Test

) 15 jet students shortly after completion of advanced jet training on T 37 and sometimes T 38 belonging to category Lansberg Type I

(*c*) 15 experienced fixed-wing pilots belonging to category Lansberg Type I

(*d*) 30 experienced helicopter pilots belonging to category Lansberg Type I.

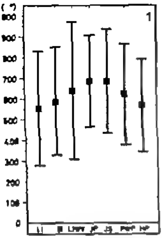
We only investigated pilots of category Lansberg Type I in order to have an exact basis of comparison towards the candidates. Moreover since few pilots belonged to other categories, no statistical evaluation was possible The pilots chosen had to fulfil several requirements (i) being otoneurologically healthy (ii) having flown at least 40 hours in the last 3 months without any prolonged non-flying period in the recent weeks, and (iii) not having flown in the last 24 hours, to prevent habituation influence.

The device consisted of an electronically steered turning chair (Toennies) and a multiscriptor (Schwarzer) Two silver electrodes, fixed about 1 cm lateral to the outer eye angle allowed measurement of the horizontal nystagmus. The subjects were sitting in a dark room with their eyes closed. They were turned first clockwise, and after 15 minutes counterclockwise round the vertical axis. After an acceleration of 2 /sec² the subjects were rotated with a constant velocity of 90 /sec until the second phase of the perrotatory nystagmus had ended and no other nystagmus was detectable. After a sudden stop we measured the first phase of the postrotatory nystagmus. The parameters investigated were: the total amplitude of nystagmus the relative difference between responses to right and left turns; the maximum slow-phase velocity; the total number of beats the duration of nystagmus and the duration of postrotatory sensation of counterrotation

RESULTS

Fig. 1 shows the alterations of the total amplitudes. Horizontally the different groups of candidates: Lansberg Type I with no vegetative symptoms (L I) Lansberg Type III with moderate (L III) and Lansberg Type IV/V with strong vegetative symptoms (L IV/V) when performing the Adroitness Test. To the right the jet pilots (JP) jet students (JST) fixed wing pilots (FWP) and helicopter pilots (HP)

It can be clearly noticed that the means of total amplitudes are higher in persons showing more vegetative symptoms (L III and L IV/V). The standard deviations of all candidates are high, most noticeable in Fig 2 with the high values of the variations-coefficients. The total amplitudes (Fig. 1) of jet pilots, however are even higher than those of candidates of T...



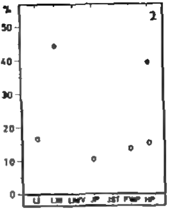


Fig. 1 Means and standard deviations of total amplitude.

Fig. 2 Variations-coefficient (●) $V = s/m \cdot 100$ (%) of total amplitudes and difference of responses to right and left-turns (O).

Fig. 3 Max. slow-phase velocity of nystagmus.

Fig. 4 Number of beats of nystagmus.

IV/V vomiting after Coriolis stimulations, although jet pilots are resistant to such stressing stimuli. Their standard-deviations are markedly smaller than those of candidates, notably best in the low value of the variations-coefficient (Fig. 2). The same results, yet with higher standard-deviations were found in jet students. It is very surprising that helicopter pilots show total amplitudes, their means being at the same low level as those of candidates of category Lansberg Type I. The variations-coefficient are markedly higher than those of jet pilots. The results of fixed-wing pilots lie half way between those of jet pilots and helicopter pilots.

Regarding Fig. 2, one sees that the means of differences between responses to right and left turns—briefly called right–left differences"—in their relation to another are similar to the results of the variations-coefficients. That means, the more vegetative symptoms observed in candidates, the higher the right–left differences. Jet pilots have markedly smaller right–left differences than candidates and have smaller differences and coefficients than fixed-wing and helicopter pilots.

The same aspect is notable as that of total amplitude, looking at Fig. 3 with the means of maximum slow-phase velocity and looking at Fig. 4 with the means of the numbers of beats. Differing from total amplitude and max. slow-phase velocity the mean values of the numbers of beats in fixed-wing pilots are lower than those of helicopter pilots.

Fig. 5 with the means of duration of nystagmus and the means of duration of postrotatory sensation again reveals higher results as a consequence of proneness to motion sickness in candidates (L III and L IV/V) and the even higher values of jet pilots. There is only a slight increase of the duration of nystagmus.

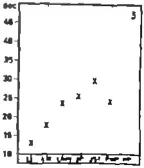


Fig. 5 Duration of nystagmus (●) and duration of postrotatory sensation ( ).

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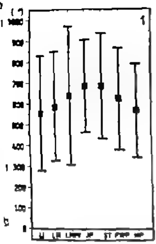

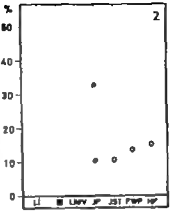

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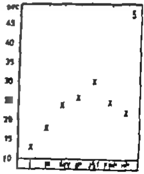

Fig. 5 Duration of nystagmus (●) and duration of postrotatory sensation (×).

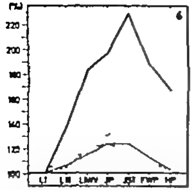

Fig 6 Alterations (in percent) of the different parameters investigated, when compared with the level of Group: L I (100%). ——— Total amplitude of nystagmus, ---- Max. slow-phase velocity· — — — Number of beats of nystagmus· .. Duration of nystagmus, ——— Duration of postrotatory sensation.

There are no lower values of that parameter in fixed-wing and helicopter pilots.

Fig. 6 shows alterations of the parameters investigated from a fixed level—here 100% is the level of candidates of category Lansberg Type I It is very interesting to see the out standing high alteration of the parameter "duration of postrotatory sensation" up to 228% Therefore this parameter is the most

Table I *Means and Standard Deviations*

A = Total amplitude ( ) B = Difference of responses to right and left turns ( ) C = Max. slow-phase velocity (°/sec) D = Number of beats E = Duration of nystagmus F Duration of postrotatory sensation (sec) G = ... age (years) N = Number of subjects.

	L I	L III	L IV V	JP	JST	FWP	HP
A	554 ±275	589 ±260	639 ±331	686 ±2_1	685 ±_49	623 ± 44	569 ±223
B	16.5 ±13	17 1 ±13	20 0 ±1_	10.4 ±10	10.7 ± 7	13 6 ± 9	15.5 ±13
C	62.4 ±__1	65.3 ±19	74.7 ±26	77.3 ±16	72.9 ±_5	68 0 ±14	64 1 ±19
D	58 6 ±19	69 1 ±19	74 ± 4	76.5 ±"6	83 4 ±23	70 4 ±26	76.7 ±"0
E	3_3 _10	36.7 ±10	37 4 ±10	39 1 ±10	42.7 ± 7	40.5 ±11	41 0 ±20
F	13.3 ± 9	18.1 ± 9	24 1 ±13	"6.0 ±11	30 0 ±1_	_4 7 ±13	22.0 ±11
G	22_	20 6	21.0	29.5	_5 0	32.2	28 6
N	30	25	30	30	15	15	30

sensitive of all. All other parameters lie cl together Contrary to what we had expect the total amplitude is one of the less sensi parameters.

Table I presents means and standard-dev tions of all parameters. We could not find a significance since standard-deviations are v high.

DISCUSSION

Three facts could be clearly illustrated.

1 Persons with strong vegetative sympto after Coriolis stimulation have higher pe rotatory ENG-responses, higher standa deviations, higher right–left differences th persons being resistant to motion-sickness

2. Jet pilots being resistant to motion-si ness have even higher ENG responses th non-flying persons with strong vegeta symptoms, but by contrast have the low right–left differences and the lowest sta dar deviations of all groups investigated. In ge vestibular responses decrease with age. It i therefore even more remarkable that ves bular responses of jet pilots with an aver age of 30 years are higher than those of ca didates with an average age of 22. This co bination of high yet fairly equal nystagm responses after right and left turns seem be an optimum adaptation to flight. Jet seem to develop a higher sensitivity and t same time a good balance of their ves system combined with a habituation of ve tative reactions to stressing rotatory s This development seems to depend more u the type of aircraft flown than upon the tent of flying experience, because jet st with an average flying time of 380 h already show results similar to those i experienced jet pilots.

3 Fixed wing pilots have lower sen and helicopter pilots have the lowest s sitivity of all other pilots.

These results are quite contrary to t Aschan (1954) who found lower values in duration of nystagmus and in the dura postrotatory sensation in jet pilots and

scribed them as vestibular fatigue, adaptation or habituation. Yet we found the duration of postrotatory sensation to be 128% higher in jet pilots than in the control group Lansberg Type I.

It seems as if two alterations are taking place in the vestibular apparatus of man, exposed to daily practice in various rotatory maneuvres: Alteration I takes place over a long period of time: a development towards higher sensitivity which means an *increase* in response. Alteration II occurs when exposed to repeated rotations at short intervals: a habituation, which means a *decrease* in response.

Finally there is the unsettled question, why pilots flying different types of aircraft reveal such different ENG-responses.

Our theory is that with a decreasing ability or necessity to use the optical system in spatial orientation there will be an increase of the sensitivity of the vestibular system.

Helicopter pilots have many reference-lines towards the horizon in their cockpit and thus can recognize tilting or rotating maneuvres very early by the use of their eyes. In addition helicopters perform low speed, low level flights and carry out fairly abrupt and immediately noticeable maneuvres. Therefore there is no need for a highly sensitive vestibular system.

Fixed-wing pilots have also good reference lines with respect to the horizon. But their aircraft, mostly transporters, commonly do not undertake abrupt maneuvres.

The visual references of jet pilots are markedly smaller than those of other pilots, especially when sitting in the very nose of supersonics. Moreover jet pilots during their training learn to estimate the angular velocity of turns.

ZUSAMMENFASSUNG

Postrotatorische ENG-Werte von Anwärtern auf die Pilotenausbildung, die keine, mäßige oder erhebliche vegetative Reaktionen auf Coriolisreize zeigen, werden mit denen von Piloten verglichen, die verschiedene Flugzeugtypen fliegen. Es konnte folgendes festgestellt werden.

a) Je größer die Empfindlichkeit gegenüber Coriolisreizen ist, desto höher werden die postrotatorischen ENG-Werte und desto größer wird der Unterschied zwischen den Werten nach Rechts- und Linksdrehung.

b) Bei Jet Piloten tritt während der fliegerischen Ausbildung eine Habituation ihrer vegetativen Reflexe auf. Gleichzeitig kommt es zu einer höheren Sensitivität und einer besseren Balance des vestibulären Systems.

c) Diese Entwicklung zu höherer Sensitivität ist geringer bei Propellerflugzeugpiloten.

d) Bei Hubschrauberpiloten ist diese Entwicklung nicht feststellbar

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Table II *Bacteriological findings in acute maxillary sinusitis 119 patients with 171 diseased sinu with 197 bacterial strains*

	Number of bacterial strains					
	Not completely opaque maxillary sinuses		Completely opaque maxillary sinuses		Total material	
	n		*n*	%	*n*	
No growth	14	23	34	30	48	28
Staphylococcus aureus	9	11	9	8	18	9
Staphylococcus albus	7	9	8	7	15	7.5
Pneumococci	15	19	37	31	52	26
Alfa-streptococci	6	8	5	4	11	5.5
Beta-streptococci	2	3	3	2	5	2.5
Haemophilus influenzae	12	15	15	13	27	13.5
Coliforms	1	1	3	2	4	2
Proteus	—	—	1	1	1	0.5
Neisseria	1	1	1	1	[illegible]	1
Aerobic diphther rods	2	3	1	1	3	1.5
Anaerob. streptococci	2	3	—	—	2	1
Anaerob. gramneg. rods	8	10	—	—	8	4
Enterococci	—	—	1	1	1	0.5

Not meningo- nor gonococci.

in the maxillary sinuses with secretion without bacterial growth is not particularly favourable.

The present material was large enough to admit comparison between two modes of treatment in diseased sinuses without bacterial growth or with pneumococci, irrigation only and irrigation combined with phenoxymethyl penicillin 2 g three times daily The treatment was introduced before the bacteriological results were known. The results as measured by number of radiological improvement points are presented in Table IV Patients with secretion without bacterial growth in the diseased sinus treated by irrigation only or by irrigation combined with penicillin perorally demonstrated an equal number of improvement points. In patients with pneumococci in the diseased sinus the addition of penicillin perorally to the irrigation does not give any significant improvement when compared with irrigation only

DISCUSSION

Most authors have not defined the conception of sinusitis used by them Sometimes the diagnosis seems to be based on the sympto sometimes on the clinical findings. In ot cases the diagnosis is established on the ba of radiological or bacteriological findings. Th results of different investigations can only b compared if a distinct definition is given Th definition in the present investigation is ra logical, only including those sinuses with ra logically demonstrated mucous mem thickening and secretion

In the completely opaque sinuses, not

Table III *Radiological findings in acute max sinusitis after various modes of treatment ra omly selected Correlation to the most frequ bacteriological findings*

	No. of sinuses	No. of improvement points after 15 days treatment
No growth	45	[illegible]
Staphylococcus aureus	17	3.4
Staphylococcus albus	13	3.0
Pneumococci	50	3.5
Alfa-streptococci	10	4.0
Haemophilus influenzae	26	[illegible]

Table IV *The improvement of acute maxillary sinusitis related to treatment*

	No. of sinuses	No. of points before treatment	No. of improvement points after 15 days treatment
Sinuses with "sterile" secretion treated by irrigation	17	4.0	2.7
Sinuses with "sterile" secretion treated by irrigation and penicillin	17	4.0	2.7
Sinuses with pneumococci treated by irrigation	19	4.0	3.2
Sinuses with pneumococci treated by irrigation and penicillin	10	4.1	3.5

closing secretion, this had to be demonstrated by irrigation.

Most clinicians consider acute maxillary sinusitis with radiologically complete opacity of the diseased sinus as a more severe condition than one with some air left. However this does not necessarily mean that the patient suffers from more severe symptoms when the diseased sinus is completely opaque. In general, the present investigation confirms this presumption. When the diseased sinuses were divided into completely opaque and those with a lesser degree of radiological changes, the only difference in symptomatology that could be demonstrated was a more frequent occurrence of purulent nasal discharge in the former group. The analysis of pain and olfaction did not disclose any difference between the groups. The present investigation could thus not confirm the finding of Hinde (1950) that headache is more frequent in patients with radiologically completely opaque maxillary sinuses.

An interesting finding is the high occurrence of dental symptoms (18%) in both groups. These symptoms naturally direct many patients' suspicion to a dental cause of the pain and may also be thus interpreted by some dentists.

The findings of the present investigation demonstrate that the symptoms as presented by the patient do not correlate particularly well with the degree of radiological changes.

The occurrence of secretion without bacterial growth or with pneumococci was a more common finding in not completely than in completely opaque sinuses. The more frequent incidence of purulent nasal discharge and of bacteria in patients with completely opaque maxillary sinuses indicates that the radiological state reflects the severity of the disease from the bacteriological viewpoint. Other bacteria than pneumococci were in general more common in the completely opaque sinuses. However even in these, the occurrence of secretion without growth was relatively high (23%). The high frequency of secretion without bacterial growth may be due to an unsuitable sampling technique or a non-bacterial infectious etiology of the disease, i.e. virus or mycoplasma in the present material. Further it may be due to allergy It was attempted to exclude this by use of the case history but in some patients the disease might have had an allergic or vasomotor etiology Finally the occurrence of secretion without growth may indicate that the secretion may remain in the sinus even after the autogenous mechanisms have overcome the bacterial invasion. The cause in these instances may be an impairment of the sinus ostium. The importance of the function of the sinus ostium in sinusitis has previously been pointed out (Drettner, 1965 1966 Zippel & Meier 1968)

Surprisingly the sinuses without bacterial growth healed slowly radiologically This may reflect an unfavourable course in the disease when the etiology is non-bacterial, i.e. myco- plasma, virus or allergy which

the mucociliary transport, or again may reflect the impaired function of the ostium in certain cases.

The finding of a high number of improvement points in sinuses with pneumococci and a low number in sinuses with Haemophilus influenzae is consistent with the clinical experience that the former is comparatively more accessible to treatment than the latter

In two groups of patients with secretion without growth or with pneumococci all patients were irrigated but half of them received high doses of penicillin perorally in addition. It is obvious that in sinuses with "sterile" secretion, the addition of penicillin does not afford any advantage over irrigation only Surprisingly the addition of penicillin perorally in cases with pneumococci, which in the present investigation were always sensitive to this antibiotic, did not give any definite radiological improvement compared with treatment by irrigation only Thus, one may question whether penicillin is the proper antibiotic to be used for the treatment of sinusitis. Further this finding again emphasizes the importance of drainage for the restitution of the diseased sinus.

ZUSAMMENFASSUNG

Die Symptome der akuten Kieferhöhlenentzündung wurden analysiert und mit den röntgenologischen und bakteriologischen Befunden vor der Behandlung verglichen Das Material wurde in radiologisch ganz verschattete und nicht ganz verschattete Sinus unterteilt. Einige nasale Absonderung kam am häufigsten in der ersteren Gruppe vor Im übrigen waren die Symptome in beiden Gruppen einander ähnlich. Sekret ohne Bakterienwachstum und Pneumococcen waren am gewöhnlichsten in nicht völlig verschatteten Nebenhöhlen, während alle anderen Bakterien im allgemeinen gewöhnlicher bei völlig verdichteten Nebenhöhlen waren. Weiterhin wurde der radiologische Heilungsverlauf im Verhältnis zu den bakteriologischen Befunden analysiert. Nebenhöhlen mit Pneumococcen hatten einen günstigeren Heilungsverlauf als solche mit Haemophilus Influenzae oder mit sterilem Sekret. Der letztere Befund unterstreicht die Bedeutung der Funktion des Sinusostiums. Diese Annahme wird auch durch folgenden Befund gestützt Die Zugabe von hohen Penicillindosen zur Spülung gab bei Nebenhöhlen mit Pneumococcen kein besseres Resultat als Spülung alleine

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DIAGNOSIS AND TNM CLASSIFICATION OF MAXILLARY SINUS CARCINOMA

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Abstract. In order to detect a malignant lesion in the maxillary sinus at an early stage, the following points should be borne in mind. Suspicion of cancer should be aroused by the presence of continuous bloody nasal discharge, buccal paresthesia, buccal swelling, ocular pain and/or toothache. One should be more suspicious of cancer in the presence of swelling of the lateral wall of the nasal cavity or bulging of the inferior nasal meatus. Radiopacity of the unilateral maxillary sinus should be watched with special attention. In many cases in which the tumour was invisible, a positive result was successfully obtained by a blind punch biopsy through the inferior nasal meatus. X-ray findings are important together with clinical findings, and by using various projections we were able to obtain the expected results.

Our TNM classification of the carcinoma of the maxillary sinus is as follows:

T1 Tumour confined to the maxillary sinus, with no evidence of bone involvement.

T2 Tumour causing destruction of the bony wall, with the external periosteum remaining intact as a capsule, and the surrounding tissue not invaded but only compressed. Minimal infiltration into the ethmoid cells and the exophytic tumour in the middle nasal meatus is included in this category

T3 Tumour infiltrating deeply into the surrounding tissue by penetration of the external periosteum.

T4 Tumour extending to the base of skull, the nasopharynx and the maxilla of the opposite side.

The validity and usefulness of our TNM classification have been demonstrated For example, the radiation effect was remarkably better in T1 2 than in T3–4. Concerning the crude survival rate there was little difference between the irradiation and operation groups at T1 or T2 but at T3 the results were far worse in the irradiation group alone than in the combined therapy group.

From 1957 to 1969 420 cases of carcinoma of the maxillary sinus were treated at Osaka University Hospital. Carcinoma of the maxillary sinus is usually suspected from the symptoms, clinical findings and radiograms and a definite diagnosis is established by histological study However diagnosis is not always easy and is very often made only after a lengthy merry-go-round of the patient among doctors, when the presenting symptoms are not remarkable.

One of the aims of this paper is to discuss the procedure for establishing a diagnosis of the disease through our experience. Once the diagnosis is established, the extent and the malignancy of the tumour are important factors in determining the therapeutic policy The international TNM classification for carcinoma of the maxillary sinus has been pending. We have presented here a classification and have studied its validity

Diagnosis

The period from onset of the disease to the first examination is shown in Table I. About half of the patients came to us within 2 months of the initial symptoms being noted. In some cases, more than a year had elapsed since the initial symptoms had been noticed. Generally speaking, the longer the period, the more extensive the lesion. However in some cases, the tumours were not so extensive as anticipated even after more than a year since the onset of the disease. Thus, the growth rate of the

Table I *Period from onset of the disease to first examination*

Period (months)	No. of cases	
1	86	20
2	127	30
3	64	15
4	38	9
5	27	6
6	34	8
7 8 9	16	4
10, 11 12	17	4
>1 year	11	3
Total	420	

tumour varied considerably from one case to another

Those cases which were previously treated in other hospitals without being recognized as carcinoma are shown in Table II 134 cases (32%) received conservative therapy polypectomy or radical operation as empyema from an otolaryngologist. 71 cases (17%) had extraction of teeth by dentists. 34 cases (8%) were diagnosed as neuralgia or periostitis by physicians of other specialities.

Symptoms at the onset of the disease and complaints at the time of first examination are shown in Table III Although main complaints were nasal obstruction nasal discharge, buccal paresthesia and buccal swelling, it was ry difficult to distinguish carcinoma from yema when presenting symptoms were hasal obstruction and or nasal discharge. the presence of buccal swelling or continuous bloody discharge, even to the slightest degree more suspicion should be aroused in favour of carcinoma

Table II *Cases which were misdiagnosed and mistreated in other hospitals*

	No. of cases	%
Otolaryngologists	134	3
Dentists	7	1
Physicians of other specialities	34	8

Table III *Symptoms of carcinoma of the maxillary sinus*

	At first examination		At onset of disease	
Symptom	No of cases		No of cases	
Nasal obstruction	290	69	147	35
Nasal discharge	277	66	109	[illegible]
Bloody discharge	202	48	84	20
Exophthalmus	160	38	13	3
Epiphora	155	37	17	4
Ocular pain	67	16	13	3
Diplopia	38	9	0	0
Buccal paresthesia	349	83	139	33
Buccal swelling	294	70	113	27
Buccal pain	164	39	71	5
Paresthesia of teeth	223	53	80	19
Toothache	122	29	46	11
Swelling of gum	59	14	21	5
Swelling of hard palate	71	17	11	3
Difficulty on opening mouth	33	8	0	0
Lymph nodes in the neck	33	8	0	0
Headache	88	1	21	5

According to our statistical study as many as 80% of patients with carcinoma of the maxillary sinus had the past history of chr sinusitis. On the other hand, 10 of Japane adults suffer from chronic sinusitis. There the chances of a person with chronic sinu to developing later carcinoma of the sinu considered 36 times as high as for a pers without chronic sinusitis. We reckon t possibility of a patient with sinusitis to de carcinoma of maxillary sinus during his l time to be 1 or 2%

The following objective findings in an ea stage of the disease were found to be im portant. Even when no tumour is found the nasal cavity careful examination sh be made in case of medial displacement of the lateral nasal wall or bulging of the infer nasal meatus. When exophthalmus is pre even to the slightest degree the physi should suspect carcinoma of the maxi sinus. If the eyeball is displaced upwards case should be considered fairly advanced. The oral vestibule should be examined not only

inspection, but also by careful palpation to detect any tumefaction of the canine fossa, the tuber of the maxilla or the zygomatic bone. The importance of posterior rhinoscopy need not be repeated. Difficulty in opening the mouth is a finding indicative of the involvement of the pterygoid muscles.

It is very important to recognize radiologically whether there is any bone destruction or not. Bone destruction in the middle and inferior nasal meati, the maxillo-ethmoidal plate, and the orbital lamina may be found particularly in an early stage. When the anterior and inferior bony walls of the maxillary sinus are involved, clinical findings are more useful than radiograms to detect the lesions. On the other hand, X ray examination is indispensable to detect lesions of the posterior superior and lateral bony walls of the maxillary sinus.

Each projection in X-ray examination has its own advantages and disadvantages in the diagnosis of paranasal sinuses. In plain X ray films, the radiopacity of the maxillary sinus is best examined by occipitonasal projection (Waters method) half axial projection is suitable to examine the posterior bony wall and axial projection is suitable to examine the involvement of the pterygoid process or the middle cranial base. The detailed examinations should be made by laminography Especially frontal laminograms at 1 centimetre intervals from 3 to 7 centimetres from the face are used to recognize the extent of the tumour Though the superior and posterior bony walls can be examined by sagittal laminography it is difficult to obtain laminograms in the same plane as on the healthy side In this sense

Table IV *Histological type of carcinoma of the maxillary sinus*

Histology	No of cases	%
Squamous cell carcinoma	392	93
Anaplastic carcinoma	18	4
Adenocarcinoma	10	2
Total	420	

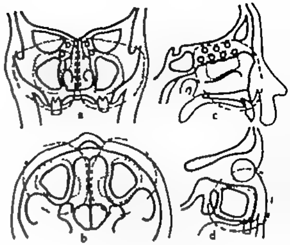

Fig 1 Schema of the borderlines between grades of the extension. ——— Borderplane between T2 and T3 – – Borderplane between T3 and T4. (*a*) Frontal section at the second premolar (*b*) Horizontal section through th. zygomatic arch. (*c*) Sagittal section at the second incisor. (*d*) Sagittal section at the pupil.

rotatory transverse laminography is considered to be extremely valuable For the planning of radiation therapy transverse sections of the head are of most practical use. In this manner the six bony walls of the maxillary sinus are examined.

Histological examination should be made by biopsy When the tumour can be seen directly in the nasal cavity or the oral cavity there is no difficulty in taking biopsy When the tumour remains invisible, blind punch biopsies through the inferior nasal meatus may give a positive determination of carcinoma. Exploratory opening of the maxillary sinus should be regarded therefore as the last resort either to confirm or eliminate the diagnosis of cancer

Histological findings of 420 cases of malignant tumours of the maxillary sinus examined in our hospital are shown in Table IV squamous cell carcinoma 94% anaplastic carcinoma 4% and adenocarcinoma 2% When carcinoma is strongly suspected from clinical findings, radiotherapy or even chemotherapy should not be delayed too long to await the definite histological

Table V *Main clinical features in each stage according to the directions of the tumour exte*

Direction of tumour extension	Grade of the tumour extension			
	T1	T2	T3	T4
Supero-medial	Tumour without bony involvement Confirmed by antrostomy	Mass [illegible] mid-nasal meatus. Slight exophth. Minimal defect of orbital wall	Deep infiltr. into ethmoid cells. Exophth. with displaced eyeball. Large defect of orbital floor	Markedly limited eye movement. Visual impairment. Defect of base of skull
Supero-lateral		Defect of superolat. wall	Defect of zygomatic bone	Defect of zygomatic arch. Defect of lat. wall of orb
Infero-medial		Bulging of inf. nasal meatus	Bulging of floor of nasal cavity. Bulging of hard palate	Large mass beyond the midline
Infero-lateral		Bulging of upper gum. Defect of inferolat. wall	Mass in upper gum	Large mass in buccal mucosa
Anterior		Swelling of cheek without adhesion. Bulg. of canine fossa	Swelling of cheek with invasion. Defect of orbital rim	Large mass in face
Posterior		Rarefaction of post. wall	Bulging of retromolar area. Defect of post. wall with fairly intact pterygoid process	Infiltr. to nasopharynx. Defect of pterygoid proc. Defect of base of sk

TNM Classification

In 1967 we presented a proposed TNM classification of carcinoma of the maxillary sinus, taking account of other tentative proposals. At first we attempted to classify maxillary sinus carcinoma into three stages on the basis of the operative methods employed, the first stage when the tumour could be extirpated by the so-called standard maxillectomy, the second stage, when complete cure was possible by the super radical maxillectomy including resection of the orbital content, the masseter muscle and the facial skin, and the third stage when radical operation was impossible as the tumour extended into the base of skull or the nasopharynx. In addition to the above-described three stages, we would now specify another stage in the classification, at which the tumour was localized only in the maxillary sinus.

The following T1–T4 were the four stages presented mainly on an anatomical basis of the tumour. Fig. 1 shows a schematic illustration of the borderlines between grades of the extension.

T *Primary tumour*

- T1 Tumour confined to the maxillary sin with no evidence of bony involvement.
- T2: Tumour causing destruction of the bon wall, with the external periosteum remain ing intact as the capsule and the surround ing tissue not invaded but only compres Minimal infiltration into the ethmoid ce and the exophytic tumour in the mid nasal meatus is included in this category.
- T3 Tumour infiltrating deeply into the sur rounding tissue by penetration of the ex ternal periosteum.
- T4 Tumour extending to the base of sk the nasopharynx and the maxilla of the opposite side.

Concerning metastasis, the TNM cla tion for malignant tumours of the b cavity by UICC was used.

N *Regional lymph nodes*

- N0- No palpable nodes
- N1 Movable homolateral nodes
- N2. Movable contralateral or bilateral n
- N3 Fixed nodes

Table VI *TNM Classification of the carcinoma of the maxillary sinus*

	T1	T2	T3	T4	Total (%)
N0	5	152	183	37	377 (90)
N1	0	10	15	12	37 (9)
N2	0	0	2	3	5 (1)
N3	[illegible]	0	1	0	1 (0)
M1	[illegible]	0	0	0	0 (0)
Total (%)	5 (0)	162 (39)	201 (48)	[illegible] (12)	420 (100)

Stage	Combination of TNM	No. of cases ( )
I	T1N0M0	5 (1)
II	T2N0M0	152 (36)
III	T3N0M0, T1–3N1 2M0	210 (50)
IV	T4N0M0 T1–4N3M0, T1–4N1–3M0	[illegible] (13)

M *Distant metastases*

M0 No evidence of distant metastases
M1 Distant metastases present

We have reclassified all of our own material since 1957 on the basis of our TNM system As shown in Table V our TNM classification was further elaborated by adding some characteristic clinical and radiological findings in each stage according to the different sites of the tumour The term "Defect" in the note was used when actual destruction of the bone was proved by X ray films.

The results of the classification of 420 cases, which were treated by us, were as shown in Table VI The majority belonged to T2 and T3 and 10% showed metastasis to regional lymph nodes at the first examination. To evaluate the validity of our classification, it was important that cases in the same grade were treated alike and showed a similar prognosis.

Table VII *Relationship between classification and type of surgical treatment*

	T1	T2	T3	T4	Total (%)
Partial extirpation	[illegible]	6	3	1	10 (6)
Total maxillectomy	1	40	23	1	65 (37)
Super-radical maxillectomy	[illegible]	38	57	4	[illegible] (57)
Total (%)	1 (1)	84 (48)	[illegible] (48)	6 (3)	174 (100)

Table VIII. *Relationship between classification and radiation effect*

	T1	T2	T3	T4	Total (%)
Remark. effect	5 (100)	72 (44)	39 (19)	10 (19)	126 (30)
Effect	[illegible] (0)	60 (37)	86 (43)	20 (38)	166 (40)
Non effect	0 (0)	30 (19)	76 (38)	22 (42)	128 (30)
Total	*5*	*162*	*201*	*52*	*420*

We have held to the principle of preoperative irradiation since 1957 The radiation source has been changed over the years. We used 200 kVp X-ray (4 000–5 000 rad/5 W) from 1957 to 1960, Cs-137 (5 000–6 000 rad/6 W) from 1961 to 1962 and Co-60 (7 000–8 000 rad/8 W) since 1963 The operation was performed after a resting period of at least 1 month. In some of the cases where there was no clinical evidence of residual tumour after the irradiation, we elected not to do the surgery but watch the patient by periodical examination of the sinus by Caldwell–Luc's antrostomy Irradiation only was given to the far advanced cases and when the patient refused operation or was medically inoperable. Altogether 174 cases had the combined therapy of irradiation and operation, and the 246 cases received radiotherapy only

The relationship between classification and type of operation in 174 cases was as shown in Table VII. A correlation was found between the type of surgery and the stage of the tumour

Table IX. *Relationship between classification and metastasis in all clinical courses*

	T1	T2	T3	T4	Total (%)
Homolat. neck	1 (20)	25 (15)	25 (12)	[illegible] (29)	66 (16)
Contralat. neck	[illegible] (0)	3 (2)	2 (1)	3 (6)	8 (2)
Lung	1 (20)	14 (9)	[illegible] (6)	3 ([illegible])	18 (74)
Bone and other	0 (0)	9 (6)	9 (4)	1 (2)	19 (5)
Total (%)	1 (20)	40 (25)	46 (23)	20 (38)	107 (25)

Table X. *Relationship between classification and 2 year crude survival rate concerning the tre— methods*

	T1	T2	T3	T4	Total ( )
Combined therapy of radiation and operation	0/1 (0)	46/84 (55)	38/83 (46)	2/6 (33)	86/174 (49)
Radiotherapy alone	3/4 (75)	29/78 (37)	30/118 (25)	5/46 (11)	67/246 (27)
Total	3/5 (60)	75/162 (46)	68/201 (34)	7/52 (13)	153/420 (36)

Table XI *Relationship between classification and 2 year crude survival rate concerning the m— stasis*

	T1	T2	T3	T4	Total (%)
N positive on the first examination	0/0	1/10 (10)	3/16 (19)	2/15 (13)	6/41 (15)
N or M positive in the clinical course	0/1 (0)	10/40 (25)	5/46 (11)	3/20 (15)	18/107 (17)

The relationship between classification and radiation effect in 420 cases is shown in Table VIII The radiation effect was assessed as follows A) Non-effective: recurrence within 3 months of radiotherapy B) Effective: recurrence between 3 months and 1 year after radiotherapy C) Remarkably effective: no recurrence within 1 year of radiotherapy As shown in Table VIII the radiation effect was obviously better in T1–T2 groups than in T3–T4

The relationship between the stages and —nal metastases as well as distant meta—s in the course of disease is shown in Table IX Metastasis to the remote organs was found in 25% in total 25% in T— gr— 23% in T3 group and 38% in T4 gr— respectively Thus the metastasis of — carcinoma occurred in far greater — than usually supposed, particularly when the extension of the tumour progressed

The crude survival rate of the 420 ca— is shown in Table X–XII The two-yea— crude survival rate was 49% in the group of combined therapy and 27% in the group of radiation alone The average of both groups was 36% When the crude su— rate was viewed in relation to the — extent the best prognosis was found — group of combined therapy for T— — in the group of radiotherapy alone f— Therefore radical operation following — radiation should be undertaken for T3 — found that a considerable number of cases — T1 and T2 could be cured by radiothera— alone. The poor prognosis of the cases — metastasis on the first examination or — course of disease is shown in Table XI — crude survival rate viewed in relation to the clinical stages is shown in Table XII The — year crude survival rate was 30 — in — of Stage II 14% in stage III — and 20 — in total, respectively

Table XII *Relationship between classification of the clinical stage and crude survival rate*

	Stage I	Stage II	Stage III	Stage IV	Total ( )
1 year	4/5 (80)	11–/157 (—5)	1–5/210 (60)	25/53 (47)	271/420 (65)
2 year	3/5 (60)	74/15– (47)	68/210 (3–)	8/53 (15)	153/420 (36)
3 year	3/5 (60)	55/135 (4–)	47/191 (25)	4/48 (8)	11–/35– (—9)
4 year	1/3 (33)	46/1–6 (37)	34/171 (20)	3/39 (8)	84/339 (25)
5 year	1/2 (50)	33/111 (30)	20/138 (14)	1/31 (3)	55/28– (20)

The validity and usefulness of our TNM classification are thus demonstrated.

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ZUSAMMENFASSUNG

Zur Frühdiagnose eines Kieferhöhlenmalignoms muß man gut auf die folgenden Symptome achten. Bei der dauernden blutigen Nasensekretion mit Wangenparästhesie Wangenschwellung und Augen- bzw Zahnschmerzen liegt der Verdacht auf einen bösartigen Tumor der Kieferhöhle vor Falls sich zusätzlich eine Vorwölbung der lateralen Nasenwand bzw des unteren Nasengangs zeigt, soll ein Malignom sehr schnell vermutet werden. Röntgenologisch muß eine homogene Verschattung der einseitigen Kieferhöhle ein Notsignal sein. Bei großem Verdacht auf ein Malignom, auch wenn kein Tumor in der Nase zu finden ist, kann eine erfolgreiche Probeexcision durch den unteren Nasengang versuchsweise durchgeführt werden. Zur genauen Lokalisation des Tumors sind die verschiedenen X-Aufnahmen am nützlichsten.

Eine Klassifizierung des Kieferkrebses nach TNM System wird vorgeschlagen.

T1 Der Tumor wird innerhalb der Kieferhöhle ohne Knochendestruktion lokalisiert.

T2 Der Tumor zerstört die Knochenwand der Kieferhöhle, jedoch bleibt die äußere Knochenhaut noch intakt wie eine Kapsel. Die geringe Infiltration des Tumors zu den Siebbeinzellen bzw eine exophytische Wucherung des Tumors im mittleren Nasengang wird in dieser Kategorie angenommen.

T3 Der Tumor bricht durch die äußere Knochenhaut und infiltriert tief in das Umgebungsgewebe.

T4 Der Tumor dehnt sich zur Schädelbasis, zum Nasenrachen bzw zur anderen Seite des Oberkiefers aus

Es wird über die Behandlungsresultate der 420 Fälle je nach der Klassifizierung berichtet. Zum Beispiel war die Wirkung der Bestrahlung besser in der T1 Gruppe als in der T3–4 Gruppe. Die Überlebensrate bei T1 2 gab keinen großen Unterschied zwischen den ausschließlich bestrahlten Patienten und den mit Bestrahlung und Operation kombiniert behandelten Patienten. Bei T3 zeigte sich jedoch ein gewisser Unterschied zwischen diesen zwei Behandlungsgruppen.

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FIBROUS DYSPLASIA OF THE JAW BONES

Analysis of Five Cases

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Abstract Five clinically typical cases of fibrous dysplasia are analysed. Histopathologic and histochemical study revealed great variability from one lesion to another and in one and the same specimen. One case showed the histologic features of fibrous dysplasia ossifying fibroma and giant cementoma. The microscopic appearance of fibrous dysplasia is affected by the age of the process and of the patient. Definitive pathologic differentiation between the benign fibro-osseous lesions of the jaw bones can be made on the basis of microscopic characteristics together with clinical findings. The best way of treating fibrous dysplasia is by conservative surgery. In one case postoperative regrowth was successfully controlled with ACTH and oxyphenbutazone

The definition fibrous dysplasia was suggested by Lichtenstein in 1938. Albright (1937) using the term osteitis fibrosa described histologically identical lesions associated with female precocious puberty and areas of skin hyperpigmentation. The syndrome is referred to as Albright's disease

Fibrous dysplasia may involve only one bone (monostotic type) or several bones (polyostotic type). Albright's syndrome is regarded as the third variety of the disease. In addition several authors have described a hereditary type of fibro-osseous lesion which affects the upper jaw bilaterally; they regard it as a form of fibrous dysplasia called cherubism. Hoppe et al. (1966) stressed that the latter syndrome should be strictly separated from other types of fibrous dysplasia whereas Odeku et al. (1969) suggested that the disease is ... a fibrous dysplasia variant, but a ... nucleated giant cell osteoblastic granulomat... lesion.

The pathogenesis of fibrous dysplasia is ... clear. Some investigators consider it to be a neoplasm (Ringertz 1938, Ash & Ra... 1949). While some think that infection ... trauma (Schlumberger 1946) are the ... causes, most authors believe the condition to be due to a developmental defect (Th... 1956, Sinha 1965, Häupl & Riedel 19..., Odeku et al. 1969, Schmaman et al. 19...

The disease is most active before pube... and becomes quiescent in adults. The c... findings show asymptomatic enlargement of the involved bone which produces fa... asymmetry. The nasal cavities, maxillary an... trum and neural canals are narrowed b... very seldom totally occluded. Labor... findings are negative; serum alkaline p... phatase can be increased in large les... Roentgenographically, the lesion is seen a... diffusely shadowed area with or without cy... appearance (Fries 1957). The parts cons... chiefly of fibrous tissue are less ra... than those with more ossification.

The gross appearance shows ... in consistency and vascularity, young le... being soft and reddish because of rich vasc... larization, old areas being hard a...

Table I *Case material*

Case	Age	Sex	Localization of lesion
1 K. S.	8	♀	Maxilla
2 S. M.	6	♂	Mandible
3 K. A.	11	♀	Mandible
4 V. E.	56	♂	Maxilla
5 K. L.	20	♂	Maxilla

and of whitish colour There is no encapsulation, but at operation the lesion can easily be distinguished from normal bone tissue. In microscopic sections there are islets of primitive bone in fibrous tissue. Three types of fibrous dysplasia can be distinguished (Smith, 1965 Dahlgren et al., 1969).

Early lesion show richly cellular connective tissue often with mitotic figures. There are tangled mass of the fibres and metaplasia of the connective tissue produces woven immature bone. Natural osseous trabeculae are rare. Giant cells are seen but there is no oesteoblastic activity

Later at the subacute stage, the connective tissue becomes less cellular and the fibres tend to occur in whorls. The bone trabeculae are thicker and lammation takes place. At the chronic stage (in elderly patients) the bone trabeculae dominate the histologic picture. Osseous trabeculae show lamination with a rim of osteoblasts. There are few connective tissue cells. This stage may progress to myxomatous degeneration (Smith, 1965)

Dahlgren et al. (1969) observed one case in which results of histopathological examinations were available for 18 years. All three histologic types of fibrous dysplasia were found during this period.

Malignant degeneration of fibrous dysplasia is rare and has been reported in 29 cases (Gross & Montgomery 1967). Twelve had received radiation therapy on an average 14 years before sarcomatous growth occurred.

Benign fibro-osseous lesions of jaw bones are rare among Schlumberger's (1946) 60 cases of fibrous dysplasia the maxilla was involved

Fig 1 Case 1 Fibrous dysplasia involving right maxilla of a patient aged 8 years.

seven times and the mandible twice. Harris et al. (1962) reported in 13 cases with monostotic fibrous dysplasia in three of which the maxilla was affected. They stated that in their 37 cases of the polyostotic variety "maxillary and mandibular involvement was not rare" The series of Dahlgren et al. (1969) consisted of 20 cases of monostotic fibrous dysplasia of the jaw bones. The ratio of upper to lower jaw involvement was 4 1 In these papers all benign fibro-osseous lesions of jaw bones are termed fibrous dysplasia. The study series of Schmaman et al. (1970), consisting of 35 benign fibro-osseous lesions of jaw bones, included 5 cases of fibrous dysplasia, 11 ossifying fibroma, 9 of giant cementoma and 3 patients in whom definite histopathologic diagnosis between the three diseases was impossible.

Fibrous dysplasia should be treated by palliative surgery In the case of extensive lesions, the parts causing cosmetic or functional disadvantage are removed, the small lesions can often be extirpated totally

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Abstract Five clinically typical cases of fibrous dysplasia are analysed. Histopathologic and histochemical study revealed great variability from one lesion to another and in one and the same specimen. One case showed the histologic features of fibrous dysplasia, ossifying fibroma and giant cementoma. The microscopic appearance of fibrous dysplasia is affected by the age of the process and of the patient. Definitive pathologic differentiation between the benign fibro-osseous lesions of the jaw bones can be made on the basis of microscopic characteristics together with clinical findings. The best way of treating fibrous dysplasia is by conservative surgery In one case postoperative regrowth was successfully controlled with ACTH and oxyphenbutazone.

e definition fibrous dysplasia was suggested by Lichtenstein in 1938 Albright (1937) using the term osteitis fibrosa, described histologically identical lesions associated with female precocious puberty and areas of skin hyperpigmentation. The syndrome is referred to as Albright s disease

Fibrous dysplasia may involve only one bone (monostotic type) or several bones (polyostotic type). Albright s syndrome is regarded as the third variety of the disease. In addition, several authors have described a hereditary type of fibro-osseous lesion which affects the upper jaw bilaterally they regard it as a form of fibrous dysplasia called cherubism. Hoppe et al. (1966) stressed that the latter syndrome should be strictly separated from other types of fibrous dysplasia whereas Odeku et al. (1969) suggested that the disease is not a fibrous dysplasia variant but a multinucleated giant cell osteoblastic granulomatous lesion.

The pathogenesis of fibrous dysplasia is not clear Some investigators consider it to be a neoplasm (Ringertz, 1938 Ash & Raum, 1949). While some think that infection and trauma (Schlumberger 1946) are the etiologic causes, most authors believe the condition to be due to a developmental defect (Thoma, 1956 Sinha, 1965 Häupl & Riedel, 1966, Odeku et al., 1969 Schmaman et al., 1969).

The disease is most active before puberty and becomes quiescent in adults. The clinical findings show asymptomatic enlargement of the involved bone, which produces facial asymmetry The nasal cavities, maxillary antrum and neural canals are narrowed, but very seldom totally occluded. Laboratory findings are negative, serum alkaline phosphatase can be increased in large lesions. Roentgenographically the lesion is seen as a diffusely shadowed area with or without cystic appearance (Fries, 1957). The parts consisting chiefly of fibrous tissue are less radiopaque than those with more ossification.

The gross appearance shows tissues varying in consistency and vascularity young lesions being soft and reddish because of rich vascularization old areas being hard and sclerotic

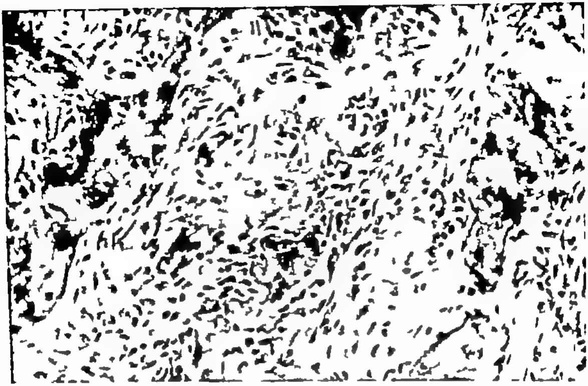

Fig. 4. Case 1. A section from an immature focus of fibrous dysplasia. Irregular osteoid bone trabeculae are seen in richly cellular connective tissue stroma. Hematoxylin and eosin, ×220.

the floor of the maxillary antrum was found in routine roentgenograms, and surgical exploration was performed. Histologically there was a fibrous stroma consisting of fairly mature collagenous bundles. Osteoid bone trabeculae, which were partly laminated, and some osteoblasts were observed. Case 5 showed a similar histological appearance, but there were also areas of active fibrous dysplasia where the bone trabeculae revealed no lamination and the connective tissue stroma was richly cellular. In addition, there were areas of fibrous tissue with deposits of basophilic material resembling cementum (Fig. 8) and presenting a weakly laminated appearance under polarized light. The matrix was highly vascularized throughout the connective tissue.

In addition to these five cases, there was one case of chronic mandibular osteomyelitis first diagnosed as ossifying fibroma. On re-examination, infiltrations of lymphocytes and plasmocytes were found in the collagenous stroma, and the case was interpreted as dentigenous chronic osteomyelitis. The bone spicules were coarse and laminated and there were irregular cement lines having a pagetoid appearance (Fig. 9).

DISCUSSION

Among fibro-osseous lesions involving the mandible and maxilla three entities are generally separated on the basis of clinical and histopathological features: fibrous dysplasia, ossifying fibroma, and giant cementoma. Many other names are used for these conditions and their mutual relations in the literature are confused.

Ossifying fibroma (osteofibroma or fibrous osteoma) is considered to be a true neoplasm originating from mesenchymal cell rests in normal bone. Clinically in X-rays or during surgery ossifying fibromas give the impression of encapsulation (Thoma, 1965; Reed,

Fig 5 A mature area of the same lesion as in Fig. 4 The stroma is not active and the osseous trabeculae are partly laminated and lined by osteoblasts in places. × 220

Fig 6 Case 3 The fine reticular fibres of an active focus of fibrous dysplasia are arranged in random fashion. Silver impregnation method of Gomori × 220.

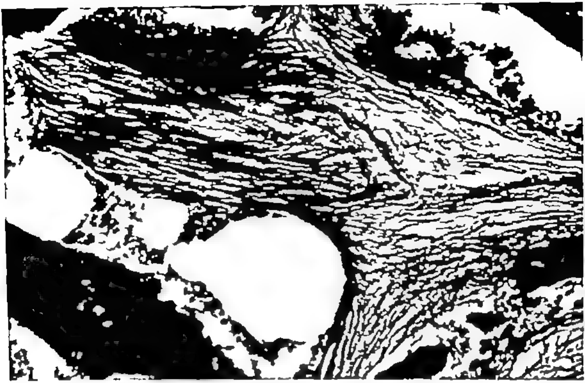

Fig. 7. A quiescent area from the same lesion as in Fig. 6. The collagenous fibres are arranged into parallel bundles. × 220.

Fig. 8. Case 5. A focus of fibrous dysplasia showing cementum-like deposits of basophilic material. Hematoxylin and eosin. × 90.

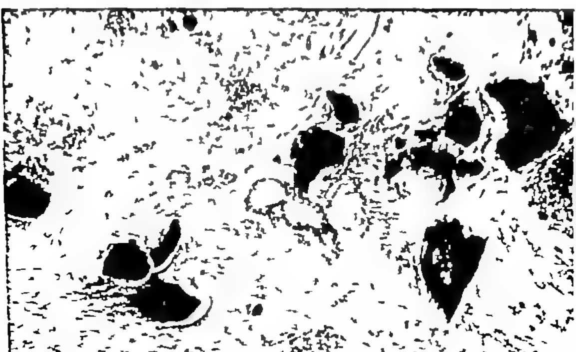

Fig 9 A section from a case of chronic mandibular osteomyelitis. There are infiltrations of inflammatory cells. The bone trabeculae show pagetoid appearance with irregular cement lines. Hematoxylin and eosin, × 220

1963 Häupl & Riedel, 1966 Schmaman et al. 1970) Histologically the bone trabeculae are lined by orderly rows of osteoblasts. Differentiation from subchronic or chronic fibrous dysplasia may be difficult. Some investigators believe that separation of these two lesions is not possible (Schlumberger 1946 Smith & Zavaleta, 1952 Fries, 1957 Sinha, 1965 Pund et al. 1965).

Histochemically Pepler (1960) found alkaline phosphatase in high concentrations in the fibroblasts in four cases of ossifying fibroma of the mandible and in one case of fibrous dysplasia of a long bone. These cells thus seem to be functional osteoblasts, not fibroblasts.

Giant cementoma shows whorling masses of fibrous tissue similar to fibrous dysplasia. It is distinguished by the droplet cementum which polarizes like lamellar bone except that the lines are thinner (Hamner et al. 1968).

All of our five cases presented fibrous dysplasia according to clinical and roentgenographic criteria. Histopathological study revealed great variations. In the three youngest patients (aged 6–11 years) the microscopic findings were those described for the active stage of fibrous dysplasia (Smith, 1965 Dahlgren et al. 1969) However there were areas of more mature bone type showing osteoblasts as described in ossifying fibroma. Many authors believe that these two lesions cannot be separated on the basis of microscopic examination alone (Smith & Zavaleta, 1952; Thoma, 1956 Reed, 1963 Häupl & Riedel, 1966). For instance Schmaman et al. (1970) reported three cases of benign fibro-osseous lesion of the jaw bones in which they could not make a definitive pathologic diagnosis of fibrous dysplasia, ossifying fibroma or giant cementoma. Our case No. 5 showed the histologic features of all three lesions. It seems, there-

fore, that only the term benign fibro-osseous lesion is justified histologically with statement of the predominant feature. Clinical diagnosis of one of these diseases should then be made from all assembled data.

The microscopic picture of fibrous dysplasia is multiform and our material supports the view of Dahlgren and his coworkers (1969) that the process is affected by the patient's age. Areas showing various stages of activity may appear simultaneously in one and the same lesion.

Fibrous dysplasia is a maturation defect of bone. Our case 1 showed in an interesting way mandibular hypertrophy on the same side as the active lesion in the upper jaw. This might indicate a developmental disturbance originating in early embryonal life, before the start of differentiation of the jaws from the first branchial arch. Fibrous dysplasia is a rare disease and ossifying fibroma and giant cementoma are even more infrequent. The histopathologic picture of the three conditions can be overlapping, because they originate from the same mesenchymal cells and preserve various differentiation features (osteoblasts or cementoblasts). In the latter two lesions proliferation of the cells results in tumour, fibrous dysplasia being a maturation defect.

Chronic osteomyelitis must be kept in mind in the differential diagnosis. One of our cases with mandibular involvement was first diagnosed erroneously as ossifying fibroma. The laminated coarse bone trabeculae with cement lines and groups of inflammatory cells in the collagenous stroma were interpreted as evidence of osteomyelitis. Dahlgren et al. (1969) reported two cases with moderate infiltration of inflammatory cells and interpreted this as a secondary phenomenon. Schmaman et al. (1970) called attention to the rule of chronic osteomyelitis in differential diagnosis and considered that a superimposed infection in ossifying fibroma and a residual focus of fibrous dysplasia are uncommon.

The small lesions of fibrous dysplasia can be extirpated totally. Large diffuse lesions are operated according to cosmetic and functional principles. Mutilating operations like mandibular or maxillary resections (Young & Putney 1968) are not indicated in benign self-limiting disease. Drugs with cortisone-like effect suppressing connective tissue formation can be helpful in some cases and situations. We have noted cessation of postoperative regrowth in one case treated with ACTH and oxyphenbutazone.

ZUSAMMENFASSUNG

Fünf klinisch typische Fälle mit fibröser Knochendysplasie im Kiefer wurden analysiert. Die histopathologischen und histochemischen Untersuchungen zeigten große Variationen von Fall zu Fall und sogar innerhalb desselben Prozesses. In einem Fall beobachtete man histologische Eigenschaften von fibröser Dysplasie, ossifizierendem Fibroma und von Zementom. Sowohl das Alter des Prozesses als auch des Patienten haben einen Einfluß auf das histologische Bild. Die Differentialdiagnose der gutartigen fibroossären Prozesse im Kiefer ist auf Grund des histopathologischen Bildes nicht immer möglich, sondern sie muß auch klinische Eigenschaften berücksichtigen. Die Therapie der fibrösen Dysplasie im Kiefer ist eine konservative Chirurgie. In einem postoperativen Rezidive wurden gute Resultate mit ACTH und Oxyphenbutazon erreicht.

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EXTRACARDIAC RHABDOMYOMA

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Abstract Extracardiac rhabdomyoma is a very uncommon tumour About 20 acceptable cases have been reported in the literature. Most of these are in the head and neck region. A rhabdomyoma removed from the submandibular region in a 36-year-old man is described. The tumour was encapsulated, multilobulated and had a total weight of 181 g. The cut surface was grey-yellow with brown areas, and the consistency soft and fleshy Light microscopy showed large round, faintly granular cells with the nuclei mostly placed in the periphery "Spider cells" were found and also myofibril-like structures. In some fibres and cells cross-striations could be visualized. There is no evidence of recurrence of the tumour after 2 years.

Extracardiac rhabdomyoma is a very uncommon tumour About 20 acceptable cases have been reported in the literature. Most of those are in the head and neck region. A rhabdomyoma removed from the submandibular region in a 36-year-old man is described.

CASE REPORT

A 36-year-old previously healthy man was referred to the E.N T clinic from his industrial doctor For a year and a half he had noted a non-tender mass in his left submandibular region He had no dysphagia or voice problems. Clinical examination revealed a soft lemon sized non-tender mass in the left submandibular region. Intra-oral and laryngoscopic examination showed a mass that elevated the left side of his tongue and vallecula. It also dislocated the epiglottis over to the right side. Nothing else unusual could be seen in the supraglottic or glottic areas. There was no obstruction of the airway Fine needle biopsy of the tumour mass was not diagnostic. Routine laboratory tests were normal.

At operation a soft, well circumscribed multilobulated tumour was found. The lower pole was easy to define but the upper portion disappeared in the soft tissues and muscles at the base of his tongue The hypoglossal nerve was markedly dislocated laterally By blunt dissection it was possible to remove a lobule of the caudal portion of the tumour Frozen section was inconclusive and it was decided to defer definitive surgery until diagnosis was established.

From the paraffin sections of the removed material a diagnosis of rhabdomyoma was made and a second operative procedure performed with complete removal of the tumour using a radical neck dissection approach. The tumour was found deep to the sterno-cleidomastoid muscle and in the submandibular region. Most of the tumour could be removed by blunt dissection Sharp dissection had to be used in the base of the tongue region. No postoperative complications except weakness of the tongue muscles on the left side probably due to a combination of excision of muscle tissue and damage to the dislocated hypoglossal nerve He has now been followed for 2 years without any sign of recurrence

PATHOLOGY

The total weight of the multilobulated tumour mass was 181 g (Fig 1) The consistency was

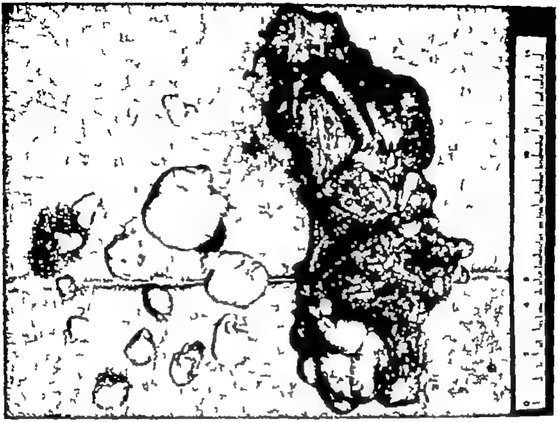
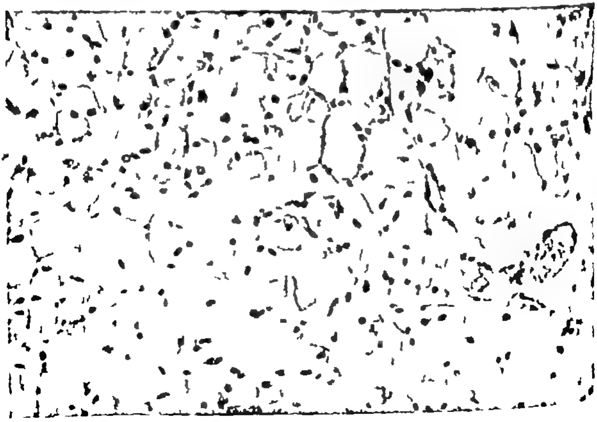


Fig 1 Gross photo of the multilobulated rhabdomyoma. Total weight 181 g.



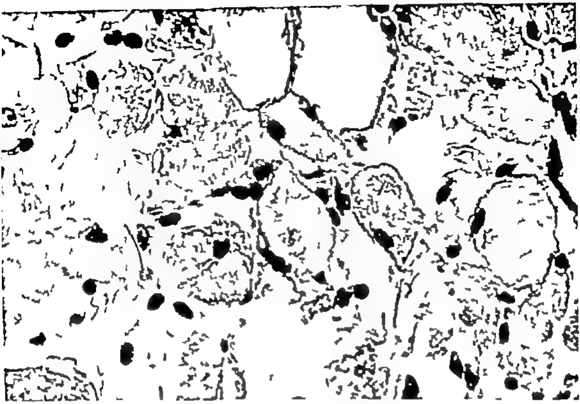


Fig. 3 Cells with vacuolated cytoplasm, peripherally placed nuclei, and prominent nucleoli. H & E, ×400.

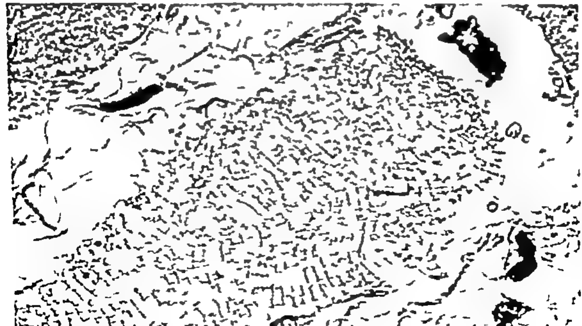


Fig. 4 Well marked cross striation in another area of the tumour. H & E, ×1,000.

Table I. *Reported accepted cases of extracardiac rhabdomyoma*

No.	Author	Year	Sex	Age	Location	Duration of symptoms	Follow-up
1	Pendl	1897	[illegible]	8 wk.	Tongue	Congenital	
2	Ritz	1926	♂	5 mo.	Tongue	Congenital	
3	De & Tribedi	1940	[illegible]				
		Case 2		13 yr	L. axilla	1 yr	No recurrence in 4 yr.
4		Case 8	♀	8 yr	Lab. maj.		No recurrence in 3 yr.
5	Beyer & Blair	1948	♂	52 yr	Sublingual	2 yr	No recurrence in 7 mo.
6	Occhinpti	1954	♂	6 yr.	Thoracic wall	[illegible] mo.	No recurrence in 21 mo.
7*a*	Parsons & Puro	1955	o	74 yr	Sternohyoid muscle	55 yr	No recurrence [illegible] 8 yr
7*b*	Goldman	1963	♂	82 yr	Larynx (separate tumour)	Autopsy—same case as 7*a*	
8	Misch	1958	♀	21 yr	Tongue	3 yr	No recurrence in 4 yr.
9	Smith	1959	♀	39 yr	Larynx	31 yr	
10	Horn	1960	♀	65 yr	R. submand. reg.	4 yr	
11	Urbanke	1962	♀	40 yr	Uterus		No recurrence in 5 yr.
12	Clinnie et al.	1963	♂	48 yr	Larynx	3 mo.	No recurrence in [illegible] mo.
13	Moran & Enterline	1964	[illegible]	67 yr	Pharynx	1 mo.	No recurrence in 33 mo.
14	Tsukada & Pickren	1965	♂	81 yr	Sublingual	3 mo.	No recurrence in 6 yr.
15	Czernobilsky et al.	1968	♂	39 yr.	Retrophar	6 yr (incomplete removal 6 years earlier)	No recurrence 1 yr after last operation
16	Battifora et al.	1969	♂	55 yr	Larynx	Many yr	
17	Assor & Thomas	1969	♂	59 yr	Mult. neck	2 yr	
18	Kay et al.	1969		64 yr	Floor mouth	2 wk.	
19	Wyatt et al.	1970	o	54 yr	Base of tongue	4 mo.	No recurrence in 5 yr.
20	Olofsson	1973	o	36 yr	Submandibular	1 / yr	No recurrence in 2 yr.

soft and fleshy and the cut surface was grey yellow with darker brown stained areas especially in the periphery. The microscopic examination revealed a uniform mat of large round cells with homogenous, faintly granular cytoplasm (Fig. 2). The vacuoles were mainly in the periphery along the cell walls. The nuclei tended to be uniform, round or oval with prominent nucleoli, and were placed at the periphery of the cells. A few cells had a centrally placed nucleus surrounded by vacuoles in a thread-like structure—so-called "spider cells". In some areas there were fibres containing myofibril-like structures. In some of the cells and fibres cross-striations could be identified. In many cells the cytoplasm contained lipid material as shown by Sudan staining. In this case special staining with phosphotungstic acid hematoxylin (PTAH) was not necessary to demonstrate the cross striation (Figs. 3–4).

DISCUSSION

The management of this case illustrates the importance of delaying definitive surgery and diagnosis of a soft tissue tumour has been established. This guiding principle has been both illustrated and emphasized by Ackerman (1968).

Rhabdomyoma is a very rare tumour if one excludes the rhabdomyomas of the myocardium that often are associated with a hamartoma complex (sebaceous adenomas, tuberous sclerosis and hamartomas of kidney and other organs) (Landing & Farber 1956).

However the extracardiac rhabdomyoma is not associated with this hamartoma complex. It is a benign sharply circumscribed tumour composed of adult-appearing striated muscle cells and fibres although it sometimes can be difficult to demonstrate cross-striations (Stout & Lattes, 1967)

The usual macroscopic appearance of extracardiac rhabdomyomas has been described as a lobulated, well encapsulated, yellow-brown tumour with a fleshy consistency Microscopic examination shows a tumour composed of round to oval cells with a pale faintly granular cytoplasm There are many large vacuoles in the cytoplasm mainly placed in the periphery The nuclei are round to oval and vesicular with prominent nucleoli, and also placed in the periphery Sometimes they are placed centrally surrounded by vacuoles in a thread-like structure—so-called "spider cells" Cross-striations are usually visible in some cells with ordinary hematoxylin–eosin staining but is accentuated by phosphotungstic acid–hematoxylin (PTAH) staining. A sudanophilic substance is usually demonstrated in the cytoplasm of the cells of these tumours. All of the above histologic features are present in our case. The results with different staining methods and the electron microscopic features are well described by Czernobilsky et al. (1968) Kay et al (1969) and Wyatt et al. (1970)

Moran & Enterline (1964) reviewed the literature and found 12 acceptable cases of extracardiac rhabdomyomas including their own. In addition to these another 8 can now be added. All these cases are listed and numbered in Table I. Case 7 had at autopsy a separate rhabdomyoma in the larynx. Two cases in Table I are congenital (cases 1 and 2) Other cases than those listed have been reported in the literature but have already been excluded by Moran & Enterline (1964) because of either incomplete documentation or they have been reclassified as granular cell myoblastomas Cross-striations have never been found in a granular cell myoblastoma and Fisher & Wechsler (1962) have presented evidence that this tumour is of neurogenic origin and derived from Schwann cells, and should be called a granular cell Schwannoma"

Of the 20 cases listed in Table I 16 occurred in the head and neck region, 1 in the thoracic wall, 1 in the uterus, 1 in the vulva and 1 in the axilla. The age ranged from 5 weeks to 81 years. There was no predilection for any special age group, but 14 cases were over 36 years of age Fourteen occurred in males, and 6 in females. In half of the cases the duration of symptoms before operation exceeded 1 year and in one case 55 years (case 7) The conclusion of this is that it seems to be a slow growing tumour Recurrence has only been reported in one case (case 15) and considered by the author to be due to incomplete removal 6 years earlier

ZUSAMMENFASSUNG

Extracardiale Rhabdomyome sind sehr seltene Tumore. In der Literatur sind etwa 70 sichere Fälle beschrieben; die meisten im Gebiet von Kopf und Hals. Es wird ein Fall von Rhabdomyom der Submandibularlagegend bei einem 36jährigen Mann beschrieben Der Tumor wurde operativ entfernt, und wog total 181 g. Die Schnittfläche war grau-gelb mit braunen Bezirken, die Konsistenz weich, fleischig. Lichtmikroskopisch zeigten sich große runde, schwach granulierte Zellen, wobei die Kerne meistens peripher lagen. Man fand auch sowohl „Spinnen-Zellen" wie myofibrilläre Strukturen. In einigen Fasern und Zellen konnte man sogar Querstreifen beobachten. Nach 2 Jahren war noch immer kein Rezidiv zu beobachten.

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CRICOTHYROID MOTOR UNITS

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Abstract. Activity of 37 cricothyroid motor units was studied in three normal subjects. Single unit discharges were analysed during phonation at several different pitches, as well as in the absence of phonation. Interspike interval analyses were obtained, showing that frequency and variability of firing were dependent upon phonatory pitch. Interspike interval analyses from sequences obtained without accompanying phonation revealed preferred spike frequencies and limited variability A U-shape function characterized the pitch-frequency relationship of a number of units. Postural adjustments were found to affect cricothyroid motor unit discharge. The technique described here using direct and continuous feedback of information to the subject offers a powerful tool for further analyses of laryngeal function.

Characteristics of motor activity in cricothyroid muscle have been described in limited fashion by a number of investigators (Buchthal, 1959; Faaborg Andersen, 1957 1965 Katsuki, 1950) Perhaps the primary function of this muscle relates to vocalization, although respiration influences its activity (Suzuki et al., 1970) A direct relationship between phonatory pitch and rate of cricothyroid single unit discharge was observed by Faaborg-Andersen (1957 1965) Katsuki (1950) has indicated that in some cases an inverse relationship holds between pitch and discharge frequency Zenker & Zenker (1960) observed cricothyroid activity at very low pitches and also at high pitches, with reduced activity in middle registers. It is unclear whether such disparate findings reflect different populations within cricothyroid muscle or whether these stem from variations in experimental methods. The previous studies have not systematically explored pitch-frequency relationships using repetitive or prolonged samples. Neither has there been careful attention to control over the phonatory pitches employed.

The present study further analyses the characteristics of single motor unit discharge of the cricothyroid muscle.

METHOD

Three human adult males served as subjects for the experiment. Sterile, insulated platinum-iridium wire (Medwire 0.0014 in.) was inserted into cricothyroid muscle following a method described by Shipp (1969) The subject was then seated in a swivel-tilt chair within a dimly lighted room Each subject participated in at least 12 experimental sessions during which unit activity was recorded.

Electrical activity was amplified by a Grass P 15 Preamplifier and displayed on one channel of a Tektronix 565 Dual Beam Oscilloscope Phonation appeared on the second channel.

Amplified electrical signals from the muscle were displayed both visually and aurally to the subject. The subject was instructed to utilize the visual and auditory signals as information to assist in securing voluntary control over the firing of a single motor unit. When the subject reported he was able to produce a single unit at a fairly constant rate

without vocalization, approximately 2 min of this spontaneous activity was recorded. Three aspects of cricothyroid unit activity were studied (1) pitch relationship (2) postural in fluences (3) "spontaneous" activity

Pitch relationships were studied in one of two ways. In the earlier sessions a pre programmed tape was activated It contained tones of the following frequencies: 140 Hz, 180 Hz, 240 Hz, and 300 Hz. Beginning at the lowest frequency each tone was repeated three times, together with the instructions to emit a sustained phonation ("ahhh") lasting approximately 20 sec. After three such episodes, the tone was shifted upward and the process was repeated. This procedure gener ated a cumulative total of 60 sec data for each reference tone

In later sessions, vocal pitch was limited to ranges in which the correlated unit activity extended from quiescence to rates at which recruitment of additional units occurred. The subject s recorded phonation was later matched to audio oscillator tones in order to determine the fundamental pitch associated with various unit discharge rates

Postural influences on unit firing were assessed by tilting the subject backward from the vertical position using both rapid and slow oscillatory movements. Unit firing was monitored throughout the procedure

Sustained unit firing in the absence of lization was examined by requiring the subject to produce unit discharges while he monitored his visual and aural signal.

Motor unit and phonatory output signals were recorded on magnetic tape for subsequent analysis. Analysis of interspike intervals was conducted using a digital computer (PDP 12) This analysis was employed both in *on-line and off-line configurations.*

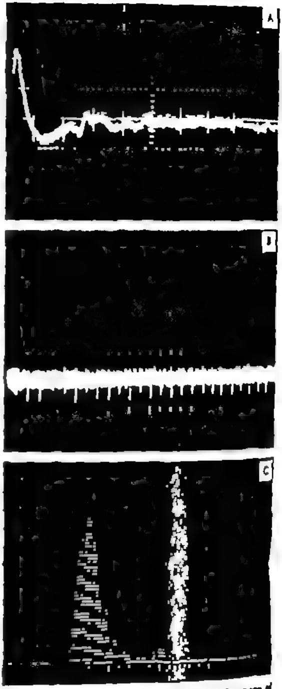


Fig 1 Cricothyroid unit activity *A* Single sweep of cricothyroid motor unit. Sweep duration 30 msec. *B* Sustained train of spikes from unit shown in (*A*). Sweep duration. 2 sec. *C* Interspike interval histogram based on epoch from which (*B*) was obtained. Modal interspike interval of approximately 80 msec. Sampling period. 256 msec.

RESULTS

Single motor units were readily isolated by each subject, provided that the audio and visual monitors were utilized. Excessive EMG present during the initial stages of each session could be reduced by appropriate attention to the monitors. Without such information, however the subjects were usually un-

able to produce a response confined to the discharge of a single motor unit.

Each subject discovered that some aspect of motor output (e.g., tongue movement, mild yawning) was capable of producing correlated single motor unit discharge Cessation of the relevant action terminated the unit discharge Occasionally the discharge occurred spontaneously (i e., during a resting or relaxed period) However the subject always found that appropriate action could serve to eliminate totally the discharge

Vocalization was found to be the optimal procedure for searching out and activating units, but most of them were found to be activated by a variety of other actions, including head movement, jaw movement, tongue movement, or respiration. In these cases the discharges of a given unit could be sustained for long periods. Under such conditions, units exhibited a "preferred" firing rate of 10–15/sec. Modification of the preferred rate could be achieved. Efforts to increase the rate above 15–18/sec led to recruitment of additional units in each case. Rates as low as 3–5/sec could be reached, but still lower rates could not be maintained. Instead, the units "stuttered" and failed to fire

A total of 37 units were isolated and studied systematically Most were diphasic in form, such as shown in Fig. 1 *A* An example of the sustained discharge of the unit appears in Fig. 1 *B* This activity was produced without concomitant vocalization, although the unit was not "spontaneously" active A further analysis of the discharge activity was made by deriving an interspike interval histogram over a cumulated 1 min sample of sustained firing. Fig 1 *C* shows the analysis for the "preferred" firing rate This is representative of the other units studied. It can be seen that the unit had a modal interspike interval of 80–90 msec. The distribution is characterized by relatively limited variability That is to say there was a high degree of regularity in the interspike als observed under this condition.

Fig. 2 demonstrates the relationship between discharge of the unit shown in Fig. 1 and phonatory activity by the subject With transient phonation, activation of the unit pre

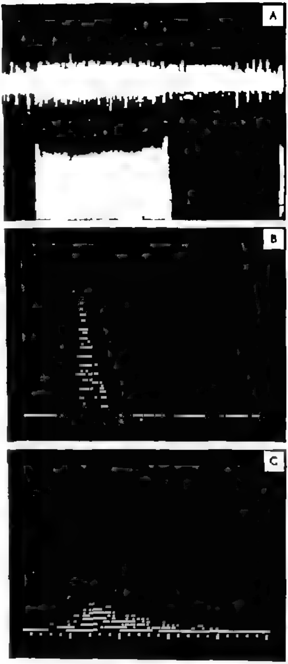


Fig 2. A Unit discharge (above) anticipates phonation (lower trace). Rate remains stable during phonation. *B* Interspike interval histogram of unit in (*A*) derived from 1 min sustained discharge without vocalization. Sampling period: 256 msec. *C* Interspike interval histogram of unit in (*A*) derived from 1 min phonation at 160 Hz fundamental frequency

ceded onset of phonation was sustained during phonation, and abruptly ceased firing at the termination of phonation (Fig 2 *A*) During the relatively brief phonation period (approximately 1 sec) the firing rate remained constant This was common for other units also and was found to be true even when prolonged phonation sequences were emitted.

The onset of spike activity (the first spike initiated the sweep in Fig 2 *A*) reliably preceded vocal output by 200–400 msec, thus making the occurrence of firing a reliable predictor of phonation

Of all units, less than 16% showed phasic relations to phonation This group was characterized by a brief discharge preceding and accompanying the early portion of vocalization Sustained phonation resulted in such units falling silent ordinarily within the period of 1–2 sec Interspike interval analyses consequently could not be obtained

Interspike interval characteristics in cases wherein unit discharge was maintained throughout the phonation period were compared with those seen during non phonatory sustained firing This analysis is shown in Fig. 2. The unit exhibited a regular discharge pattern in the absence of phonation (Fig. 2 *B*) Phonation modified the discharge in the manner illustrated in Fig. 2 *C* In this condition *the interspike intervals became more variable* despite the fact that a fixed vocal pitch was emitted.

Simultaneous examination of vocal pitch and discharge frequency of the motor units revealed clear correlations between the two measures. An example of the pitch-frequency relationship is shown in Fig. 3 which represents interspike interval histograms derived in association with several pitches. Phonation of "ahhh" to match an oscillator tone of 160 Hz was related to sporadic single unit discharges.

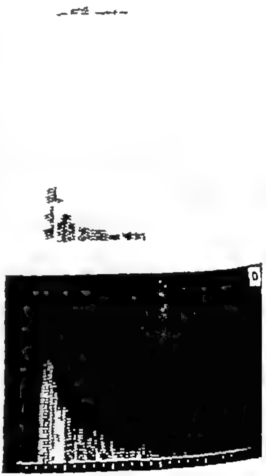
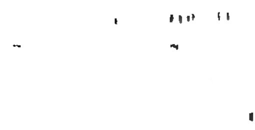


Fig 3 Interspike interval histograms of cricothyroid unit obtained during phonation at different fundamental frequencies *A* 160 Hz; *B* 180 Hz; *C* 240 Hz; *D* 300 Hz. Sampling period: 256 msec.



4 Effect of postural shift upon discharge of cothyroid unit. Upper trace: Tilt backward to proximately 60° off vertical. Lower trace: Return upright from approximately 20° off vertical. Sweep 2 sec.

es slightly lower than 160 Hz were not nied by discharges of this unit Suc vely higher pitches, however revealed ore clearly correlated unit activity At 180 (Fig. 3 *B*) the interval histogram exhibited definite peak, indicating a degree of re d firing. Further regularity was evident 240 Hz (Fig. 3 *C*) At this pitch the inter pike variability was reduced, and at a still igher pitch of 300 Hz (Fig. 3 *D*) there was en greater consistency in the firing intervals. yond 300 Hz there was recruitment of additional units.

Not all units exhibited a monotonic relationhip between discharge frequency and phonaory pitch as demonstrated above. In fact, it common to observe firing by the motor nit at rather low pitches (100–140 Hz), as well as at the higher pitches. In these cases, midange phonatory pitches were characterized by y limited discharge of cricothyroid units. Consequently there was a U-shape functional relationship between vocal pitch and discharge frequency

Amplitude of phonation proved to be und to unit discharge characteristics. There were no consistent changes in firing rate or in variability as the subject shifted from softest to loudest modulations of a given pitch.

Posture of the subject was found to exert a significant effect upon unit discharge Units were ordinarily silent in the quiet, resting subject if he sat upright or leaned slightly forward. If the subject was tilted backward in his chair it was possible to activate and control unit discharge frequency

An example of the modulation of unit discharge associated with positions is shown in Fig 4 The figure indicates that tilting the entire head and trunk backward to 60 off vertical results in the activation of several units As the process reverses, however the discharge slowly terminates, leaving but one unit active Further movement toward the upright position eliminated firing, and the system became quiescent (20 to 0) Virtually all of the units of the study exhibited a similar response pattern.

DISCUSSION

Our placement of electrodes in cricothyroid muscle can be assumed on the basis of the technique which followed that of Faaborg Andersen (1957) and Shipp (1968). The results are sufficiently consistent with previous work (Buchthal, 1959 Faaborg Andersen, 1965 Katsuki, 1950 Zenker & Zenker 1960) to warrant a conclusion that circothyroid muscle units were reached Since virtually all units exhibited similar functional characteristics, the assumption is additionally strengthened

It has been reported that cricothyroid units are active even when respiration or phonation is suppressed (Faaborg Andersen, 1965) However Katsuki (1950) noted that an electromyographic analysis of activity in cricothyroid muscle failed to show sustained discharge unless the subject phonated. Our observations lead to an intermediate conclusion. That is to say the technique employed may markedly influence the results Given a situation in which visual and aural display of unit activity is made available to the subject, the information can be used either to assist in eliminating tension in the muscle or to assist in sustaini

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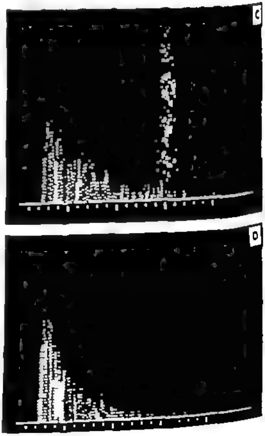

Fig 3 Interspike interval histograms of cricothyroid unit obtained during phonation at different fundamental frequencies. *A* 160 Hz; *B* 180 Hz; *C* 240 Hz; *D* 300 Hz. Sampling period. 256 msec.

discharges were found. Movement backward beyond the vertical position was accompanied by activation of units. The rate of unit discharge varied directly with the degree of backward tilt. It appears that a degree of hysteresis occurs, since there is often multiunit activity elicited immediately on tilting backward, whereas return to the upright position produces a gradually declining unit discharge rate which does not disappear until the subject returns almost to the vertical position. From such data it can be seen that the analysis of laryngeal motor units requires attention to postural factors which can bias their discharge properties.

ZUSAMMENFASSUNG

Die Aktivität von 37 motorischen Einheiten des m. cricothyroideus wurde an drei normalen Personen untersucht. Die Entladungen einzelner Einheiten wurden sowohl während der Phonation von Tönen verschiedener Höhe als auch ohne Phonation untersucht. Die Interspike-Intervall-Analyse ergab, dass die Frequenz und die Variabilität der Entladungsrate von der Tonhöhe abhängig war. Die Interspike-Intervall-Analyse von Aufnahmen ohne Phonation ergab bevorzugte Entladungsraten und begrenzte Variabilität. Eine U-förmige Funktion beschreibt die Tonhöhenbeziehung für eine Anzahl von Einheiten. Änderungen der Körperposition beeinflußten die Entladungsrate von motorischen Einheiten des m. cricothyroideus. Die hier beschriebene Technik, die einen direkten und kontinuierlichen Rückfluß von Information zu der Versuchsperson ermöglicht, stellt eine große Hilfe für die weitere Analyse der Funktion des Kehlkopfes dar.

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EVALUATION OF UNDERGRADUATE TEACHING IN OTOLARYNGOLOGY

U Sarala and J Tarkkanen

From the Educational Committee and the Otolaryngological Hospital University of Helsinki Helsinki Finland

(Received December 2, 1971)

Abstract Objective tests have been compared with essay tests for the purpose of evaluating undergraduate teaching in otolaryngology From the point of view of both students and teachers, objective tests may be preferable to essay tests. However teachers should bear in mind that good multiple-choice questions are not compiled at a moment s notice but usually require painstaking work. Careful analysis of the test questions is required since each of them should be valid and reliable.

In recent years the increase in number of medical students has brought about changes in the examinations for the degree of Licentiate in Medicine in Finland As long as the number of examinees was 30 or fewer per year the final examination was conducted orally by the Professor in each subject This was also so in the case of otolaryngology at elsinki University until—with the increase number of undergraduates—essay tests and, ater multiple-choice questions were introduced Examination correctly understood is an essential component of instruction (Niemi, 1965) However those who teach medicine are unfortunately so much preoccupied by the planning of instruction and the load of practical teaching work that the critical evaluation of various examination methods is thrown wholly into the shade We therefore wish to give a description of various types of tests.

Tests can be divided into two main types: so-called objective tests and essay tests. Objectivity in this context means that scoring should be as simple as possible and that all scorers should arrive at the same result

OBJECTIVE TEST TYPES

The *validity* of test questions means that they should measure what they are intended to measure The *discrimination index*, which shows the difference between the groups of good and poor examinees, can be used as a measure of validity With the aid of this index it can be established whether a test is capable of differentiating between good and poor students

The *reliability* indicates the extent to which casual factors are involved in a test situation. For instance, variations in the mode of answering can be considered casual effects: the answers of one person can be based on knowledge, another's on what he has heard, yet another's on imagination.

The above mathematical indices are calculated by means of a statistical test analysis, which will not be dealt with more closely in this article

The third factor worth considering in the *level of difficulty* of the test question can be expressed in terms of percentage i.e as the percentage of examinees who have answered correctly to the question concerned

1 *Alternative responses*

Example

a) The unit of sound pressure is the decibel (dB)

Right Wrong

(Draw a circle around the correct alternative)

2. *Multiple-choice questions*

Example

a) A patient has had impaired hearing in one ear for many years. There has been no discharge and no vertigo. The affected ear shows no response to the caloric test and there is corneal anesthesia on the affected side. The probable diagnosis is:

a) Ménière's disease
b) Cholesteatoma
c) Acoustic neurinoma
d) All three combined

(Draw a circle around the correct alternative.)

3 *Matching*

These tests consist of several items of information, and they should be matched two and two together

Example

a) Match disease with suitable medication.

Nystatin	1 Epiglottitis
Ampicillin	2. Pseudomonas infection in the ear
Colistin (Colymycin)	3 Candidiasis
	4 Acute otitis media

4 *Classification*

Example

	Discrimination score	
	definitely impaired	impaired slightly or not at all
Otosclerosis		
Presbyacusis		
Acoustic neurinoma		
Chronic otitis		
Noise injury		

(Put in space provided.)

5 *Ranking*

Example

Rank the following lung lobes according to the number of segments. Write No. 1 after the lobe containing the most segments, No. 2 after the lobe with the next greatest number of segments, and so on.

a) Right middle lobe of lung A ________
b) Right lower lobe of lung B ________
c) Left lower lobe of lung C ________
d) Right upper lobe of lung D ________

6 *Short questions*

Example

State the amount of impairment allowed for the hearing to be within the so-called social limit of hearing.

Guessing

The effect of guessing associated with objective test types can be minimized by using a method in which the examinee indicates, after each answer how sure he feels about his own answer for instance as follows:

- absolutely certain (AC)
- fairly certain (FC)
- don't know (DK)

A student receives 2 points for a correct answer stated to be absolutely certain, but if an answer considered to be absolutely certain proves to be wrong, 4 points are deducted. A fairly certain and correct answer gives the examinee 1 point, and correspondingly 1 point is deducted for a wrong answer. "Don't know" equals 0 points.

This system complicates scoring to some extent. If the test includes a sufficient number of questions (e.g. 70–100 alternative responses and 40–60 multiple-choice tests), the effect of guessing is of little practical significance.

ESSAY TESTS

These can be divided into short and long essays, and subjects for essays.

Examples:

1 Which paranasal sinuses border the orbit (short essay).
2 Anatomy of the vestibular organ and testing of its function (long essay).
3 The noise problem (subject for essay).

The marking of essays almost always presents possibilities of error which makes the grading fairly arbitrary. The following advice may help, though only slightly, to modify such errors.

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2. Read quickly through a number of answers written by various examinees and thereby supplement the ideal answer.

3. Have another look at the ideal answer before marking a student's answer so as not to allow the preceding student's answer to affect the marking.

4 Always deal with the same question in each paper before proceeding to the next question

5 Go through each answer twice varying the order arbitrarily

6 Stick to the following principle of classification If you use a 5-point scale, place the answers at first reading into five heaps the best in heap 5 the second best in heap 4 and so on. The second reading is started for instance from heap 5 now considering whether the answer is so good that it should be moved into heap 4 or perhaps poor enough to go into heap 2. In this way each heap is examined and, where necessary answers are shifted into another heap

SUITABILITY OF THE TESTS IN OTOLARYNGOLOGY

When compiling the test papers it is good to consider whether one wishes to measure mainly pure memorized knowledge, e.g. some facts belonging to the physician's basic store of knowledge, or the power of clinical application, i e. the ability to apply facts correctly

Factual knowledge can be most easily measured by using the above objective tests. If desired, the examinees can be given specially prepared punched cards, on which they can enter the correct answer for instance by piercing the card with the pen point. Such cards can be scored in a few seconds by using a computer and thus the time taken by scoring is reduced to a minimum.

Clinical application can also be measured by objective tests, even though these are much more difficult to compile than when testing only factual knowledge Power of application can be measured for instance by using a *case report* followed by a number of multiple-choice questions The case report can be presented either written or on transparencies films, TV or by using all these media combined. The questions may be concerned with etiology diagnosis, proposed treatment, etc. The aim is primarily to make the student familiar with situations that may arise in practical work. This type of test is usually felt by the students to be meaningful and motivating. If the number of objective tests is small, there is good reason to use the method for minimizing the effect of guessing described above.

Essay tests can also be used for measuring ability of clinical application, but marking is then unduly time-consuming and inexact. One possibility is to use for instance 40 alternative responses or 20 multiple-choice questions, followed by a number of essay tests, and mark the essays only in case that the student copes well with the initial questions.

In our experience, the undergraduates at Helsinki University who sit for the final examination in otolaryngology prefer multiple-choice questions to essay tests. This increases the amount of work the staff has to do because the time taken by the preparation and grading of good multiple-choice questions may be ... be longer than that required for both the preparation and marking of essays (Hubbard & Clemans, 1961) It might be a good idea in the future to consider increasing inter-university co-operation in the field of un... teaching, for instance by exchanging ... multiple-choice tests between universities.

ZUSAMMENFASSUNG

In der Publikation wird der Unterricht der L... daten der Medizin durch Vergleich der objektiven Prüfungen mit den erzählenden sc... lichen Prüfungen bewertet. In den letzten Ja... wurde die erzählende schriftliche Prüfung durch Mehrwahlaufgaben in zunehmendem Maße er... Mann sollte immer sehr sorgfältig beim Ausar... und beim Bewerten der Mehrwahlaufgaben sein, d... sie sowohl valid als auch zuverlässig bleiben.

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THE SINUSOIDAL GALVANIC BODY-SWAY RESPONSE

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(Received November 15 1971)

Abstract. Galvanic body-sway responses to sinusoidal stimulus currents were obtained from eight neuro-otologically normal young adult male subjects. In all subjects, the body swayed sinusoidally in response to the sinusoidal stimulus. The most effective stimulus frequency differed in different subjects and ranged from 0.025 Hz to 0.200 Hz. The responses of all subjects declined abruptly as frequency was increased above 0.200 Hz and were barely recognizable at 0.800 Hz. Trapezoidal galvanic-response wave form and sinusoidal frequency response appeared to be related. Subjects with a.c. trapezoidal responses had negative sinusoidal stimulus-response phase angles at low frequencies and a low-frequency cutoff. Subjects with d.c. trapezoidal responses had positive phase angles at low frequencies and relatively flat frequency-response curves across the low-frequency range. Clinical cases demonstrating depression of the sinusoidal galvanic body-sway response coincident with depression of the trapezoidal response are presented. However, test-retest variability of the sinusoidal response is much greater than that of the trapezoidal response. Therefore, clinically the sinusoidal response *should be regarded as providing only* a qualitative supplement to the quantitative results provided by the trapezoidal response.

In previous studies of the recorded galvanic body-sway response (Coats, 1972 *a b c*) we used a constant current turned on and off with a variable rise-fall time (a "trapezoidal" wave form) We wish here to report an investigation of body-sway responses to a sinusoidally varying current.

The results should help elucidate the nature of the galvanic body-sway response, and thence of the balance and-equilibrium system, and should also help in applying galvanic body sway to clinical testing.

METHODS

Eliciting and recording the sinusoidal galvanic body-sway response

The subjects stood with feet together (shoes on) and eyes closed. Current was applied by means of an aluminum-foil electrode affixed to the mastoid area with electrode paste and surgical tape. A standard EKG electrode on the ipsilateral forearm completed the circuit.

Stimulus current was generated by the constant-current generator used in previous studies (Coats, 1972 *a*), except that the instrument was modified to produce a current which varied according to an externally generated wave form (in this study a sine wave).

Stimulus current was monitored with a microammeter Before each application of the sinusoidal current, a small biasing current was adjusted to produce equal positive and negative excursions. Peak-to-peak amplitude was 0.16 mA ($\pm$0.8 mA)

The body-sway responses were recorded on a rectilinear pen-writing recorder by means of a potentiometer transducer which was attached to the subject's chest with a thread.

Subjects and stimuli

Eight young male subjects without detectable neuro-otologic abnormalities were studied

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two groups. Three subjects constituted a preliminary group used to determine the general nature of the response to the sinusoidal stimulus and to establish the stimulus parameters for subsequent, more thorough study

The second group (five subjects) was stimulated with a series of frequencies ranging from 0.025 Hz to 0.800 Hz. Each subject attended five sessions and at each session was stimulated by each frequency in the series (order randomized) Stimulus durations were adjusted so that 15–20 cycles were delivered to each ear during each session Thus, during the five sessions, we obtained at least 75 cycles of body-sway response at each frequency

Each subject was also given a trapezoidal stimulus of 0.8 mA with a rise fall time of 0.4 sec and total duration of 10.4 sec. We gave 15 of each of the four possible stimuli (right ear + left ear + right ear − left ear −) to each subject.

RESULTS

Wave form of the sinusoidal galvanic body-sway response

Fig. 1 shows records of body-sway responses to sinusoidal galvanic stimuli of different frequencies. In order to get some idea of what these responses would look like if random body movements were averaged out we superposed individual cycles by tracing from the original records. The result is shown in Fig. 2. Figs. 1 and 2 demonstrate that 1) the body sways sinusoidally in response to a sinusoidal galvanic stimulus, 2) as with the trapezoidal stimulus, the body sways toward the positive stimulus and away from the negative stimulus, and 3) the amplitude of the response is different at different frequencies.

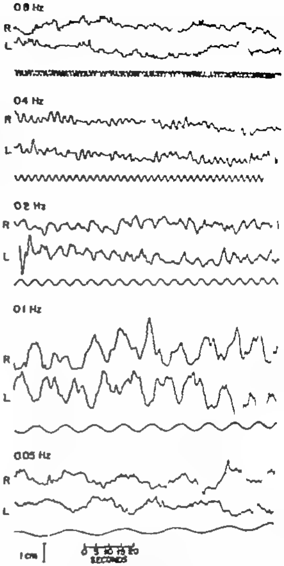

Fig 1 Body-sway responses to sinusoidal galvanic stimuli of different frequencies. As with all records shown, upward pen deflection corresponds to sway to the right. Responses from the right ear are labeled "R" and those from the left ear are labeled "L". Stimulus wave forms are shown at the bottom. Upward pen deflection represents positive polarity at the stimulated ear. Peak-to-peak stimulus current was 0.16 mA (±0.8 mA).

The frequency response of sinusoidal galvanic body sway

We used the following procedure to obtain quantitative measurements of response amplitude. First, we measured the time relationship between each stimulus peak and the corresponding response peak ("lag-lead time"). We then calculated phase angles from lag-lead time and plotted their frequency distributions. Modal (most frequently occurring) phase angles were determined from the frequency distributions. Fig. 3 shows frequency distributions of phase angles obtained from the same subject whose records are shown in Figs. 1

and 2. Modal phase angles obtained from the frequency distributions shown in Fig. 3 are plotted in Fig. 2 as broken lines.

The peak-to-peak amplitude of each response half-cycle at its modal phase angle relative to stimulus was then measured. For

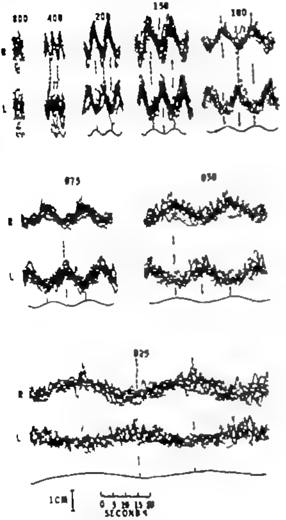

Fig. 2. Superimposed traces of sinusoidal galvanic body sway of normal subject no. 2 from one test session. These records were obtained by hand-tracing from original records similar to those shown in Fig. 1. Responses from the right ear are labeled *R* and those from the left ear are labeled *L*. Dashed lines show modal response peaks determined from the frequency distribution shown in Fig. 3. Stimulus frequency is shown above each pair of responses. Stimulus wave form is shown below each pair of responses (upward deflection represents positive polarity at the stimulated ear). Peak-to-peak stimulus current was 0.16 mA (±0.8 mA).

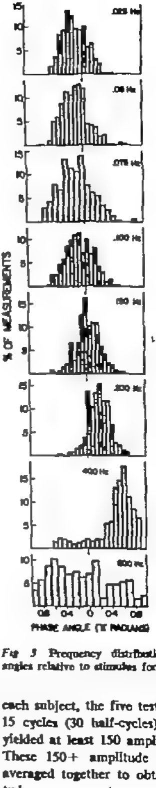

Fig. 3. Frequency distribution of response phase angles relative to stimulus for subject no. 2.

each subject, the five test sessions of at least 15 cycles (30 half-cycles) at each frequency yielded at least 150 amplitude measurements. These 150+ amplitude measurements were averaged together to obtain the final amplitude measurement.

Frequency-response curves were obtained

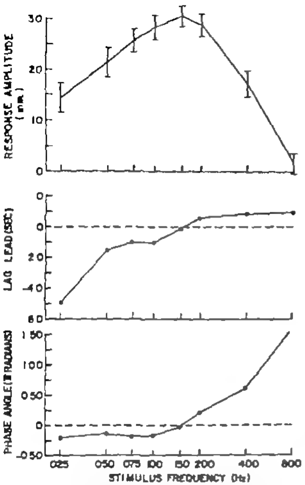

Fig. 4. Frequency response of sinusoidal galvanic body sway of subject no. 2 (same subject shown in the preceding three figures). Peak-to-peak response amplitudes (—) were measured at modal lag-lead points, as determined from the frequency distributions own in Fig. 3 and averaged across all runs. Cross represent 2 × theoretical standard deviation of e) means ($\sigma/\sqrt{N}$). Temporal relationship of re se to stimulus is plotted in terms of lag-lead time center) and phase angle (bottom). These are modal values determined from the frequency distributions shown in Fig. 3.

from 7 of the 8 subjects. Figs. 4 and 5 illustrate the two types of curve obtained. The amplitude curve in Fig. 4 (from the same subject shown in the preceding three figures) has a distinct peak at 0.15 Hz. Also the phase angle is negative at low frequencies. In contrast, in Fig. 5 the amplitude curve is flat, and the phase angle is positive across the low frequencies.

Four subjects showed the drop in response amplitude and negative phase angles at low frequencies illustrated by Fig. 4, and 3 subjects showed the constant response amplitude and positive phase angles at low frequencies illustrated by Fig. 5.

Certain aspects of the frequency-response curves were strikingly similar across all subjects. In all seven subjects, the phase angle (whether positive or negative) stayed relatively constant at low frequencies, while the lag-lead time changed. At about 0.150 Hz, the phase angle began to increase abruptly and the lag-lead time became relatively constant. Also, in all subjects, response amplitude declined abruptly as frequency was increased above 0.200 Hz.

In the second group of 5 subjects, we attempted to relate height and weight to peak frequency. However, as shown in Table I, the five subjects did not provide sufficient data to correlate peak frequency with height and weight.

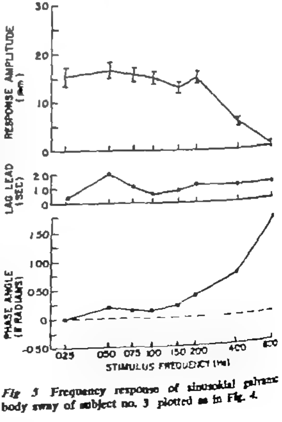

Fig. 5. Frequency response of sinusoidal galvanic body sway of subject no. 3, plotted as in Fig. 4.

Table I. *Relationship of peak frequency and subject's height and weight*

Subject	Peak frequency	Height	Weight (lb)
1	.075	5 11	188
2	.150	5 11	178
3	.050	5 7	151
4	.200	6 0"	205
5	.025	5 10"	208

Relationship between frequency response of sinusoidal sway and wave form of the trapezoidal response

One could explain the apparent tendency of the responses of some subjects to "lead" the stimulus by assuming that the responses were governed by rate of change of the stimulus rather than by its amplitude. If this were so, then the response would appear to lead the stimulus by $^1/_4$ cycle (the differential of the sine is the cosine). If a delay of less than $^1/_4$ cycle were then added, the response would appear to lead the stimulus by some amount less than $^1/_4$ cycle, as do the actual responses.

If the negative phase angle is due to a tendency to respond to rate of change of the stimulus, then a square-wave galvanic stimulus given to a subject with negative sinusoidal phase angle should produce a response resembling that of an a.c.-coupled system. Thus, these subjects should sway at the onset of the stimulus, then return to baseline while the stimulus is still on, and finally at stimulus cutoff should sway briefly in the opposite direction. In contrast, subjects with positive phase angles throughout the frequency range ought to have square-wave responses resembling a d.c.-coupled system.

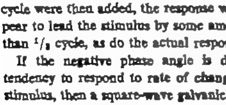

Fig. 6. Superimposed traces of trapezoidal responses of subject no. 2. Upward deflection represents sway to the right. Stimulus polarity is shown in the center. Stimulus wave form is shown at the bottom. The stimulus was a 0.8 mA current with rise-fall time of 0.4 sec and total duration of 10.4 sec.

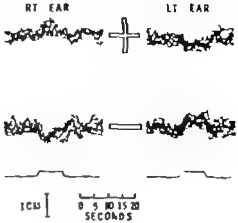

Fig. 7. Superimposed traces of trapezoidal responses of subject no. 3. Stimulus was the same as given to subject no. 2.

Because of the importance of the square-wave response's wave form in assessing the nature of the sinusoidal response, all subjects from whom complete frequency-response curves were obtained were also given trapezoidal stimuli with short rise-fall times (approximating a square wave). The trapezoidal responses of the subjects whose frequency responses are shown in Figs. 4 and 5 are shown in Figs. 6 and 7 respectively. All subjects with negative phase angles at low frequencies had a square wave response resembling an a.c.-coupled system similar to that shown in Fig. 6. All subjects with positive phase angles at low frequencies had a "d.c." square-wave response similar to that shown in Fig. 7.

Clinical application of sinusoidal galvanic body-sway

If each cycle of the sinusoidal stimulus produced an independent response, then the sinus-

more likely since the body-sway response is in the direction expected of a direct response to electrical stimulation of the vestibular nerve i.e. a positive stimulus would be expected to inhibit resting discharge of the vestibular nerve, which would produce sway toward the stimulated side, and vice versa for a negative stimulus.

2. *Response at high sinusoidal frequencies.* We have noted that, in contrast to low frequency responses, high frequency responses were quite similar for all subjects, showing an abrupt decline in response amplitude and a relatively constant time lag which resulted in an abrupt increase in phase angle with increasing frequency. One suspects that at high frequencies the sinusoidal galvanic body-sway response is governed by the body's physical characteristics i.e. the body's mass limits the rate at which it can be accelerated.

ZUSAMMENFASSUNG

Von acht neuro-otologisch normale junge erwachsene Männer wurden schwingende galvanische Körperbewegungen durch sinusförmige Erregungsströme erhalten. Alle Versuchspersonen reagierten auf die sinusförmige Erregung mit sinusartige Körperbewegungen. Die höchst wirksamste Erregungsfrequenz war unterschiedlich bei den einzelnen Versuchspersonen und lag in einem Bereich von 0,025 Hz bis 0,200 Hz. Die Reaktionen aller Versuchspersonen nahm sprunghaft ab bei einer Frequenzerhöhung über 0,200 Hz und war kaum noch oberhalb 0,800 Hz zu erkennen. Trapezartige Wellenform der galvanischen Reaktion und sinusartige Frequenzreaktion scheinen abhängig von einander zu sein. Versuchspersonen mit Wechselstrom-trapezförmige Reaktionen hatten negativ sinusförmige Erregungsreaktionsphasenwinkel bei niedrigen Frequenzen und einen Niederfrequenzabklingungspunkt. Versuchspersonen mit „Gleichstrom" trapezartigen Reaktionen hatten positive Phasenwinkel bei niedriger Frequenz und relativ flache Frequenzreaktionskurven im Niederfrequenzbereich. Klinische Fälle welche Unterdrückung der sinusartigen galvanischen Körperbewegungsreaktionen gleichzeitig mit einer Unterdrückung der trapezartigen Reaktion aufweisen werden vorgeführt. Es ist aber die Unterschiedlichkeit der einzelnen Untersuchungen bei mehreren Versuchen sehr viel grösser als bei den trapezförmigen Reaktionen. Daher sollen, klinisch gesehen, die sinusartige Reaktionen nur als qualitative Ergänzung zu den gegebenen quantitativen Ergebnissen aus den trapezartigen Reaktionen betrachtet werden.

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ON THE CHANGE IN THE ACOUSTIC IMPEDANCE OF THE EAR AS A MEASURE OF MIDDLE EAR MUSCLE REFLEX ACTIVITY

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Abstract Middle ear muscle activity recorded as change in the acoustic impedance of the ear was correlated to the EMG and the change in the cochlear microphonics elicited by the middle ear muscle contractions. The experiments were performed on lightly anesthetized rabbits. The three methods were equally sensitive as measures of the middle ear muscle reflex responses within a couple of dB. The amplitudes of the impedance change and the rectified and integrated EMG were linearly related and usually reached saturation below 125 dB SPL. The change in the cochlear microphonics differed from the change in the impedance in that it did not reach a maximum below 125 dB SPL. It was also shown that the m. tensor tympani contributes very little to the total impedance change under normal condition. On the other hand, it gives distinct changes in the impedance when the stapedius muscle is paralysed. Opening the acoustic bulla was found to increase the effect of contractions of the middle ear muscles on the acoustic properties of the ear resulting in greater changes of the CM and of the impedance.

Determinations of middle ear muscle activity have become widely used in studies of peripheral and central auditory functions in man (for review see Jepsen, 1963) The acoustic middle ear reflexes have been utilized for the same purpose in some animal studies (Kato 1913 Lorente de Nó & Harris, 1933 Kobrak et al. 1935 Kobrak, 1957 Simmons, 1964 Borg, 1971).

The introduction of methods for recording middle ear muscle activity as changes in acoustic impedance of the ear has been of great importance for the utilization of these reflexes in studies of auditory functions in man (Metz, 1951 Møller 1961 *b* 1962, Feldman & Zwislocki, 1965). The physiological interpretation of the acoustic impedance change is in many ways uncertain. The relationship between the impedance change elicited by middle ear muscle activity and more direct measures of such activity as the electromyogram (EMG) and the change in cochlear microphonics (CM) has not been sufficiently established (cf Simmons, 1962, Jepsen, 1963 Fisch & Schulthess, 1963 Djupesland, 1967 Lidén et al., 1970).

The aim of the present study was to compare the acoustic impedance change with the EMG and the cochlear microphonics change elicited by middle ear muscle reflex activity in acute experiments on rabbits. The influence of opening the acoustic bulla as well as the relative contribution of the m. stapedius and m. tensor tympani reflexes to the total impedance change was also analysed. The experiments were performed on lightly anesthetized rabbits and the impedance change was recorded with a method developed by Møller (1960 1961 *b*).

METHOD

The experiments were performed on adult rabbits of the small chinchilla strain. Recordings of the EMG were made on 7 rabbits and measurement of the cochlear microphonics

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on 6 rabbits. The influence of opening the bulla was investigated in 14 rabbits and the contribution of the m. tensor tympani to the total impedance change in 6 rabbits. Additional observations on the change in the cochlear microphonics and the impedance change were made on 2 decerebrate cats.

Recording of the middle ear reflex activity

Impedance change The relative impedance change at 800 Hz was recorded simultaneously in both ears in response to acoustic stimulation of either ear The same method was used both in non-anesthetized and in narcotized rabbits. The method has been described elsewhere in greater detail by Møller (1960, 1961 *b*) and Borg & Møller (1968) The amplitude of the impedance change at the end of the stimulus tone (0.5 sec duration) was measured and expressed in percent of the maximal impedance change obtained. The stimuli were 2.0 kHz pure tones (rise time to 90% and decay time to 10% of maximal amplitude were both 2 ms) varied in 4 dB steps up to 120 to 125 dB SPL (re. 0.0002 μbar) Four stimulus response (SR) curves, two for ipsilateral and two for contralateral stimulation based on two measurements at each sound intensity were used to describe the reflex responses.

Electromyography (EMG) of the m. stapedius and the m. tensor tympani was obtained with bipolar electrodes made of lacquered insect pins (impedance at 1 kHz 15–50 kΩ). The tips were separated about 2 mm in the longitudinal direction of the muscles. The signals picked up by the electrodes were fed through a cathode follower to a Grass P 6 pre-amplifier After band-pass filtering (200 Hz to 14.0 kHz) the signal was tape recorded (Revox G 36) and visualized on an oscilloscope. The integrated responses were obtained by low-pass filtering the rectified muscle signals during play back Active low-pass filters of third degree, i.e. attenuation rate of 18 dB/octave and with a cut-off frequency variable between 10 and 25 Hz were used.

Cochlear microphonic potentials (CM) were recorded with a unipolar silver ball electrode placed in the round window niche. The reference electrode was placed in the m. masseter The measuring tone was the same as that used in the impedance recordings (800 Hz). The intensity of this tone was 78 dB SPL and it yielded a CM of 200–400 μV peak-to-peak. The linearity of the CM was tested by changing the amplitude of the 800 Hz tone in 6 dB steps and it was found to be satisfactory between 60 and 78 dB SPL. After amplification with the same equipment as for the EMG the signal was band-pass filtered through filters identical to the ones used for impedance recordings (center frequency 800 Hz, bandwidth 100 Hz) tape recorded and visualized in the same way as for the EMG. During playback the CM was fed through the same 800 Hz filter displayed and recorded on film.

Surgical and experimental procedure

The reflex activity of the non-anesthetized animal was recorded one day before the operation. Before surgery the animals were narcotized with Pentobarbital-Na intravenously and intubated (Pyrex No 3 tube) after surface anesthesia in the pharynx and larynx (Xylocain Spray® Astra). The general anesthesia was rather superficial (an initial dose 25–30 mg/kg). One-and-a-half to 2 hours after initiation of the anesthesia, the reflex thresholds were found to be 10–25 dB above those in non-anesthetized conditions. In about half of the experiments additional doses of pentobarbital had to be administered after about 4 hours. The experiments were usually completed within 4 to 5 hours.

The animals were fixed in a headholder after the pressure points had been infiltrated with local anesthetics. The skin was incised after infiltration with a local anesthetics (Xylocain® 2% Astra) and the bulla was reached from the ventral side by blunt dissection along the medial side of the internal pterygoid muscle of the left side. Bilateral recordings of the reflex activity (impedance

change) were made before and after the bulla was opened. If there was any sign of blood in the bulla, 1–2 drops of Heparin (5 000 IU/ml) were instilled to facilitate removal of the blood by suction (no. 12 Record hyperdermic needle)

The cochlear microphonics and the impedance change were recorded simultaneously It was observed that placing the EMG-electrodes on the muscles slightly changed (probably increased) the impedance of the ear and decreased the impedance change due to the muscle activity Consequently the EMG was recorded alternating with the recording of the impedance change. After the electrodes were placed in the middle ear only the contralateral ear was stimulated. During the CM recordings the hole in the bulla was closed with small wads of absorbing paper soaked in heavy vaseline Closing and opening of the bulla could be done repeatedly without influencing the electrode position.

Most of the experiments were made on the m. stapedius alone or on the two muscles working together The isolated m. stapedius activity was recorded after cutting the m. tensor tympani with a pair of small spring scissors. The influence of the isolated m. tensor tympani on the impedance change and the CM-change was studied in only one rabbit whose m. stapedius had been denervated earlier by extracting the facial nerve through the stylomastoid foramen (cf Kato, 1913). EMG recordings of the m. tensor tympani were performed in 5 cases.

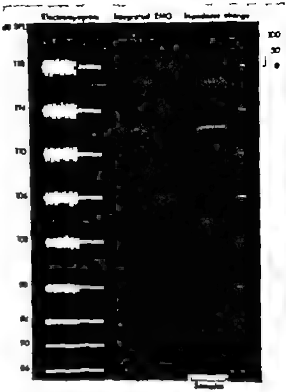

Fig. 1. Activity of the isolated m. stapedius in response to contralateral stimulation with a 0.5 sec duration of pure tone of 2.0 kHz. EMG (left column), rectified, integrated EMG (low pass filtered, ■ Hz, middle column) and impedance change (right column). Scale at upper right shows relative response amplitude for impedance change and integrated EMG in per cent of maximal obtained response. Bulla open. Reflex threshold was 70 dB SPL before anesthesia.

RESULTS

Sensitivity

Fig. 1 shows the EMG response (left column) and the rectified integrated EMG (middle column) recorded from the m. stapedius. The right column shows the impedance change of the isolated m. stapedius reflex. These recordings were made in immediate succession. The stimulus was a pure tone of 2.0 kHz in the contralateral ear The sound intensity is given by the legend numbers to the left. In these recordings the bulla was open. As is seen in Fig. 1 (90 dB) the EMG activity was recorded below the threshold for the impedance change. This was a common finding and the muscle activity expressed by motor unit potentials could be distinguished at an average of 2.9 dB (standard deviation (S.D.) = 2.9 dB) below any measurable change of the impedance. The sound intensity necessary to evoke a response of 10% of the maximal amplitude of the integrated EMG and 10% of the maximal impedance change was, however nearly the same. The mean difference between the corresponding two values was 0.7 dB

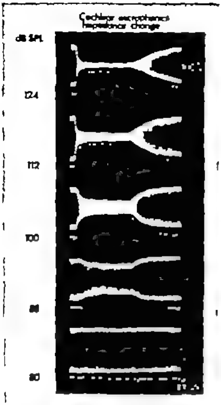

Fig 2 Simultaneous recordings of CM at 800 Hz (white area) and impedance change (broken line). Crossed total reflex elicited with 2.0 kHz stimulation. Bulla open. Threshold before anesthesia was 70 dB SPL.

(S.D = 1 0 dB) the lower intensity referring to the EMG

Fig. 2 shows simultaneous recordings of the changes in the amplitude of the cochlear microphonics and in the acoustic impedance of the ear in an experiment where the m. stapedius and m. tensor tympani were both intact (total reflex) and the bulla open. The stimulation was a contralateral pure tone of 2.0 kHz.

The threshold for a change in CM was in this case identical to that of the impedance change. Generally the impedance change was a slightly more sensitive measure of middle ear muscle activity than was the change in CM (average difference was 1 1 dB S.D = 1 0 dB at *10% of maximal change)*

The recordings in the 2 cats showed an equally good accordance between the threshold for the change in the impedance and the cochlear microphonics.

Linearity

Impedance change compared with EMG Fig. 3 shows a typical example of a pair of stimulus–response curves of the contralateral m. stapedius reflex. The amplitude of the rectified and integrated EMG (25 Hz low-pass filter) recorded from the m. stapedius (broken line) is shown together with the acoustic impedance change (continuous line). The bulla was open. It is seen that the shape of the stimulus-response curves is very similar. The relative response amplitudes were nearly identical and both the EMG and impedance change curves approached saturation at the highest sound intensity used. A close correspondence between the shape of the curves was regularly found. In no case did only the impedance reach a plateau.

Impedance change compared with CM In Fig. 4 the stimulus–response relations for the change in CM and impedance are shown. The CM change is expressed as equivalent decrease of intensity of the measuring tone of 800 Hz (in dB). In the left graph both the m. tensor

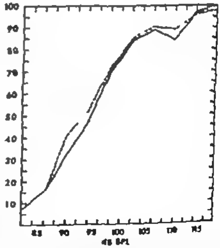

Fig 3 Relative amplitudes (in per cent of maximal obtainable response) of impedance change at 800 Hz (—) and integrated EMG ( ). Isolated m. stapedius reflex. Contralateral stimulation with 2.0 kHz pure tone of 0.5 sec duration. Bulla open. Reflex threshold before anesthesia was 68 dB SPL.

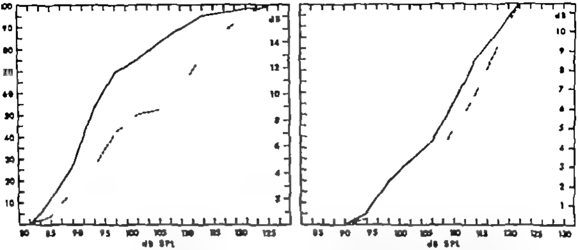

Fig. 4. Relative change of impedance (—) and equivalent change in CM ( ) at 800 Hz. Responses of the total reflex (left graph) and the isolated m. tensor tympani (right graph). Stimulus 2.0 kHz in contralateral ear. Bulla open. Left ordinate shows percentage of maximal change for both impedance and CM. Right ordinates show dB equivalent decrease in CM amplitude. Threshold before anesthesia was 70 dB SPL (left graph) and 82 dB SPL (right graph).

and the m. stapedius were intact (bulla closed) whereas in the right graph only the m. tensor tympani was intact (bulla opened). It is seen that the cochlear microphonic change was an approximately linear function of stimulus intensity up to 125 dB SPL. The impedance change was, however saturated at lower intensities when both the m. stapedius and m. tensor tympani were contracted (left graph), but not when the m. tensor tympani was activated alone (right graph).

Temporal characteristics

The onset of the EMG activity in the m. stapedius can regularly be observed in the records after shorter time delay than the change in the impedance (Fig. 1). Quantitative comparisons of the latencies are difficult to make since the onset of the impedance change is gradual.

The time course of onset of the impedance change and the change in the CM did not differ significantly (Fig. 2). No obvious difference in the latency of the changes of CM and impedance have been observed, and only minor differences in the temporal characteristics. It should be mentioned that the smoothing filters used in CM and impedance change recordings were identical.

The temporal pattern of the integrated EMG and the impedance change differed considerably (Fig. 1 middle and right columns). Although the onset was about the same at least for the high intensities, the relaxation was slower for the impedance change than for the EMG. The impedance change thus indicated a temporal integration of the reflex response could not be simulated by a linear low-pass filter. The after-discharge, often preceded by a "silent period" is not prominent enough to give the integrated EMG a sufficiently slow decay.

Influence of opening the bulla on the reflex recordings

Opening of the bulla led regularly to a change of the static acoustic impedance of the ear at 800 Hz which had about the same magnitude as that obtained during maximal reflex activity before the opening. This was val-

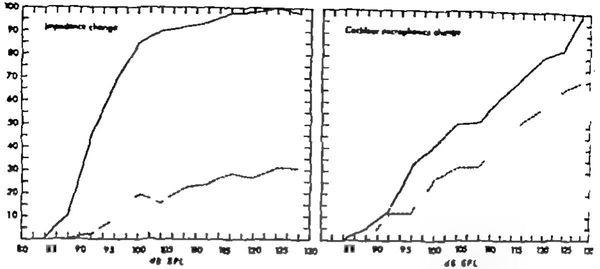

Fig 5 Relative impedance change (left graph) and change in CM (right graph). Continuous line: bulla open. Broken line: after closing the bulla. 100% denotes maximal obtained impedance change for open bulla and right hand ordinate shows equivalent chan in CM amplitude. Contralateral stimulation with . kHz. Reflex threshold before anesthesia was 70 d SPL.

id both when the bulla was opened by removing its bony wall and when the wads were removed. The amplitude of the CM at 800 Hz was increased by 6 to 12 dB Fig 5 shows the impedance change (left graph) and the CM change (right graph) elicited by contralateral stimulation at 2.0 kHz before (continuous line) and after (broken line) closing the hol in the bulla. After closing the bulla th maximal impedance change is decreased t 30–50% of the maximum value obtained whe the bulla is open. The shape of the normaliz SR-curve is, however usually the same. Th change of the CM (right graph) is also smalle

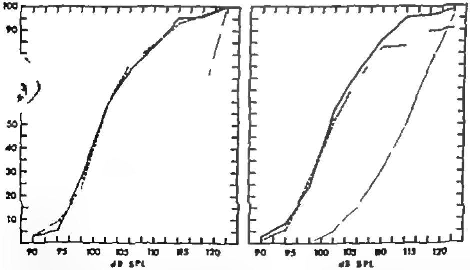

Fig 6 Relative impedance change before (—) and immediately after ( ) cutting the m. tensor tympani tendon. Two rabbits, contralateral stimulation 2.0 kHz. 100% denotes maximal obtained impedance change in each ear The dotted line shows the relative amplitude of the integrated m. tensor tympani EMG Threshold before anesthesia was 70 dB SPL (le graph) and 88 dB SPL (right graph). EMG in th right graph is from a third animal reflex thresho was 68 dB SPL.

when the bulla is closed. No maximum is reached within the sound intensity range used but the slope of the SR is slightly decreased.

Contribution of the m. tensor tympani to the stimulus response curve of the impedance change

In the rabbit with normal middle ear reflexes, both the m. stapedius and the m. tensor tympani respond to sound. The relative contribution of the m. tensor tympani to the total impedance change was investigated in acute experiments in 8 animals. In Fig. 6 two examples are shown of the impedance change before (continuous lines) and immediately after sectioning the m tensor tympani (broken lines) The dotted lines show relative amplitudes of the integrated EMG of the tensor tympani before the tendotomy The EMG shown in the right graph, is from another animal. No change was observed in the static impedance as a result of the tendotomy The maximal obtainable value of the impedance change showed no or only very slight decrease after tendotomy The stimulus–response curves of the total reflex consequently represent in very large measure only the activity of the m. stapedius. The m. tensor tympani activity was seen as an impedance change only after denervation of the m. stapedius (Fig. 4)

DISCUSSION

The sensitivity of the impedance change in recording middle ear muscle activity

The results of the present study indicate that the threshold for the middle ear reflex activity can be determined with about the same sensitivity in recordings of 1) changes of the acoustic impedance at 800 Hz, 2) changes in the CM potentials at 800 Hz, and 3) EMG activity Motor unit potentials are, however frequently observed without detectable changes in the acoustic properties of the middle ear According to the only comparable study available (Simmons, 1962), the impedance change is 10 to 15 dB less sensitive as a measure of middle ear muscle contraction than is the change in CM A fairly large volume, enclosed between the impedance measuring device and the ear drum as used by Simmons, may however have decreased the sensitivity of the recordings considerably (Djupesland, 1967) Jepsen (1963) compared the m. stapedius reflex thresholds by direct observation and by recording impedance changes in two patients with perforations of the eardrum. The differences were not greater than 5 dB in both directions. Fisch & Schulthess (1963) compared the EMG thresholds and the thresholds for visual observation in two patients under local anesthesia. The thresholds for the EMG were usually 5 to 10 dB lower than the visual thresholds.

Linearity of impedance changes as a measure of middle ear reflex activity

The stimulus response relationship of the EMG of the m. stapedius and the relative impedance change of the ear were found to be nearly identical. Both appear to reach a plateau at about the same intensity The EMG can however be recorded for stimuli a few dB below the value where any influence of the muscles on the acoustic properties can be seen

The integrated EMG in leg muscles has been found to be proportional to the developed muscle force (Bigland & Lippold, 1954). Tension measurements of the m. stapedius have been performed in rabbits by Wersäll (1958) Detailed comparisons with the data of Wersäll are not possible due to differences in the stimulus sound frequencies used Wersäll used 1 0 kHz stimulation. There is, however general agreement between the shape of the stimulus response curves representing tension and those obtained in the present study showing EMG and impedance change.

In contrast, the change in sound transmission (change in CM) through the middle ear is nearly a linear function of sound intensity and does not reach a plateau in the range of sound intensities used in the present study (see also Wever & Vernon, 1955 Simmons,

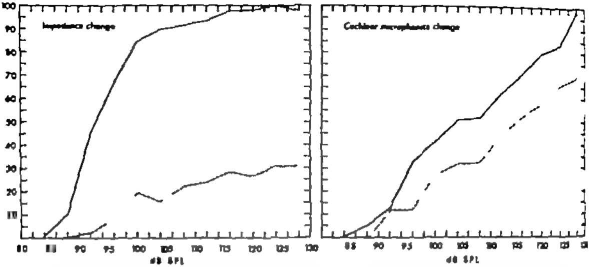

Fig. 5. Relative impedance change (left graph) and change in CM (right graph). Continuous line: bulla open. Broken line: after closing the bulla. 100% denotes maximal obtained impedance change for open bulla and right hand ordinate shows equivalent cha[nge] in CM amplitude. Contralateral stimulation with [2.0] kHz. Reflex threshold before anesthesia was 70 [dB] SPL.

id both when the bulla was opened by remov ing its bony wall and when the wads were re moved. The amplitude of the CM at 800 Hz was increased by 6 to 12 dB. Fig. 5 shows the impedance change (left graph) and the CM change (right graph) elicited by contralateral stimulation at 2.0 kHz before (continuous line) and after (broken line) closing the ho[le] in the bulla. After closing the bulla th[e] maximal impedance change is decreased [to] 30–50% of the maximum value obtained wh[en] the bulla is open. The shape of the normaliz[ed] SR-curve is, however, usually the same. Th[e] change of the CM (right graph) is also smal[ler]

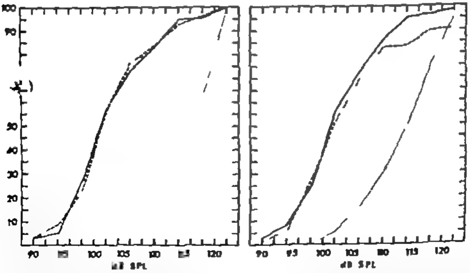

Fig. 6. Relative impedance change before (—) and immediately after ( ) cutting the m. tensor tympani tendon. Two rabbits, contralateral stimulation 2.0 kHz. 100% denotes maximal obtained impedance change in each ear. The dotted line shows the relative amplitude of the integrated m. tensor tympani EMG. Threshold before anesthesia was 70 dB SPL (le[ft] graph) and 63 dB SPL (right graph). EMG in th[e] right graph is from a third animal: reflex threshold was 68 dB SPL.

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Animals with inherited deafness have been known for millenniums and have been investigated for more than a century An impressive number of mutants of different species now known (Altmann 1950 Deol, 1968) By light microscopy the cochlear degenerative processes may be divided into two patterns—the cochleo-saccular and the scala media type.

In the former type first described by Scheibe in 1891 not only the organ of Corti but also the stria vascularis were completely degenerated, and the scala media collapsed with obliteration of the endolymphatic space Examples of mutants with this type of final endocochlear appearance are the deaf Dalmatian dog, the deaf white cat and the deaf white mink (for ref see Ernstson 1971)

In animals showing the cochlear degenerative process of the scala media complex type, the final picture is characterized by a total loss of the organ of Corti but with only scattered patches of strial atrophy and with the endolymphatic space well preserved Examples of this type are the two strains of the waltzing guinea pigs (Lurie 1939 1940, 1941 Ernstson 1971) The link between the defective gene(s) and the observed cochlear degeneration has not been established in any of these animals Different parts of extra and endocochlear

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	The vessel of the tympanic lip
Scala tympani	
Collecting venules	The limbus vessels
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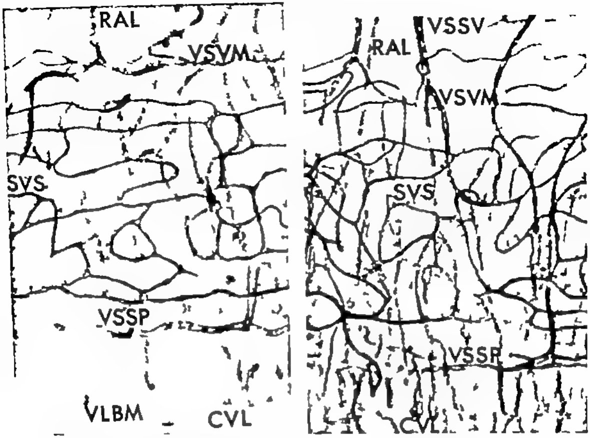

Fig. 1 Vascular anatomy of the external wall basal turn, of a young normal guinea pig (*left*) and from a 63-day-old waltzing guinea pig (*right*). Observe the similarity *RAL*, radiating arterioles; *VSSV* the vessel of the scala vestibuli; *VSVM* the vessel at the vestibular membrane; *SVS* stria vascularis; *VSSP* the vessel of the spiral prominence; *VLBM* the venules at the basilar membrane *CVL*, collecting venules.

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One possible mechanism of the endocochlear degeneration could be a defective oxygen supply resulting from an alteration in the cochlear blood vessels. However a systematic examination of all cochlear vessels is not available in any of these animals. Only examination of the condition of some of the cochlear vessels have been published, e.g. of the stria vascularis and occasionally of the vas spirale

The problem of the deafness in these animals has even broader aspects. The histopathological findings in animals have counterparts in man, i.e. the so-called cochleo-saccular degeneration. Furthermore by a comparison of the sequence of degeneration in the cochlear vessels related to the endocochlear degeneration it is possible to elucidate the hitherto unsolved question of the oxygen supply to the organ of Corti Some authors have found a parallelism between the degeneration of the stria vascularis and the organ of Corti. They therefore suggested that the organ of Corti was supplied by the stria vascularis (v Lennep 1910· Grüneberg et al., 1940) However most authors could not demonstrate a correlation between the changes in the stria vascularis and those in the organ of Corti (Meng, 1933 Lurie, 1941 1942, Nachlas & Lurie, 1951 Deol, 1956 Saunders, 1965 Kikuchi & Hilding, 1967).

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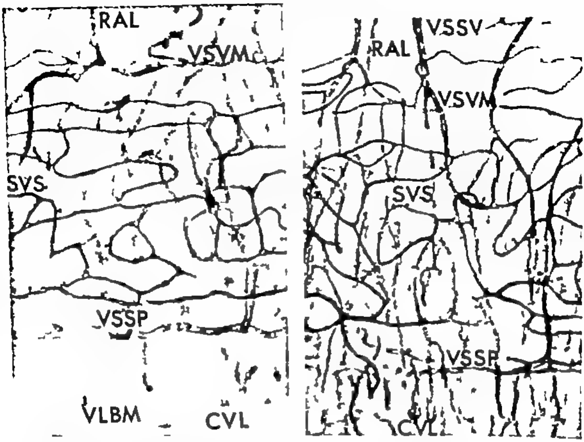

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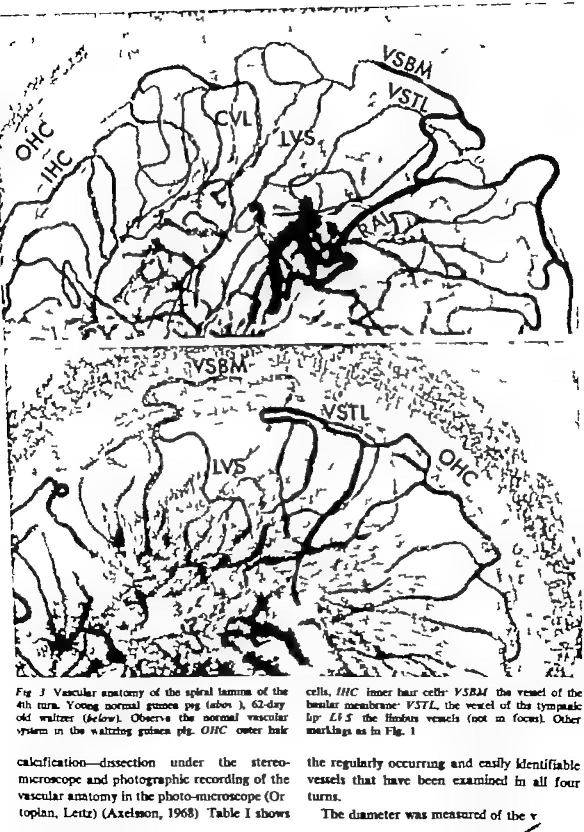

Fig. 3. Vascular anatomy of the spiral lamina of the 4th turn. Young normal guinea pig (*above*), 62-day old waltzer (*below*). Observe the normal vascular system in the waltzing guinea pig. *OHC* outer hair cells, *IHC* inner hair cells; *VSBM* the vessel of the basilar membrane; *VSTL*, the vessel of the tympanic lip; *LVS* the limbus vessels (not in focus). Other markings as in Fig. 1.

calcification—dissection under the stereomicroscope and photographic recording of the vascular anatomy in the photo-microscope (Ortoplan, Leitz) (Axelsson, 1968). Table I shows the regularly occurring and easily identifiable vessels that have been examined in all four turns.

The diameter was measured of the v

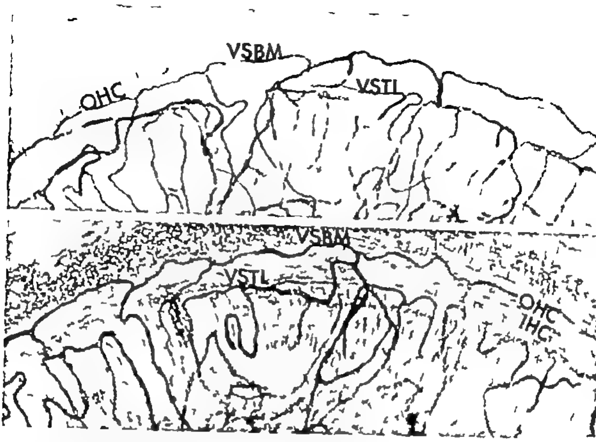

Fig 4 Vascular anatomy of the spiral lamina of the 2nd turn. Young normal guinea pig *(above)*, 37-day old waltzer *(below)*. Normal vascular anatomy in the waltzer despite severe degeneration of the organ of Corti. Markings as in Fig. 3

the basilar membrane and the vessel of the panic lip The vascular density (i e vessel gth/tissue area) of the stria vascularis was asured. The material was analysed statistic ally according to conventional methods. The level of significance was 95 %

RESULTS

Morphologic changes in the cochleae of the waltzers could easily be discerned by phase-contrast microscopy The most common morphologic changes were a degeneration of the hair cells and Huschke s dents. Further a common finding was a somewhat uneven distribution of pigment and disturbance of the regular pattern of the surface cells in the stria vascularis. The occurrence and the extent of the changes varied greatly from turn to turn and were in general most marked in the second and third turns.

The vascular anatomy of the cochlea however appeared normal at all ages in the waltzers in the external wall (Figs. 1 7), in the spiral lamina (Figs 3 4) and in the spiral ganglion (Fig. 5) The vascular pattern in the young animals, with a moderate degree of hair cell degeneration and measurable hearing function (Fig 6) was similar to that in older completely deaf animals (Fig. 7) There were no occlusions or ruptures of larger vessels or capillaries. The particular vascular anatomy of the cochlear apex and of the basal end was similar to that of the normal guinea pig. As in the normal animals, however there were regional differences in the vascular pattern in some animals.

In general, the arterial side was somewhat

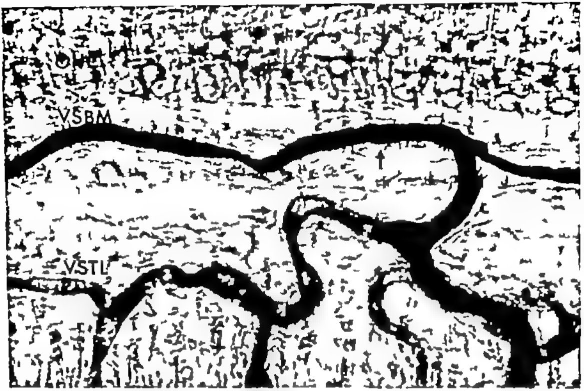

Fig 5 Above: Capillaries of the spiral lamina in a 24-day-old waltzer Granular material (*arrows*) of unknown origin surround the vessel of the basilar membrane (*VSBM*) and the vessel of the tympanic lip (*VSTL*) in the immediate neighbourhood of the outer hair cells (*OHC*), that demonstrate a moderate degree of degeneration. *SL*, spiral lamina. *Below:* Capillaries of the spiral ganglion of a 51-day-old waltzer Normal vascular anatomy

better injected than the venous. In the external wall the contrast injection was often more successful in the scala vestibuli and the scala media than in the scala tympani. Parts of the external wall were segmentally less well contrast injected in both the normals and the waltzers. An increased amount of pigment occasionally surrounded the vessel of the spiral prominence (Fig. 8), which is also found in the aged, normal cochlea. The vascular density of the stria vascularis (vessel length/tissue area) was normal (Table II)

Segmentally in the spiral lamina parts of the radiating arterioles and collecting venules may be less well injected in both the normal and the waltzer cochlea. The [illegible] lary vessels in the spiral [illegible] tunnel of Corti and in [illegible] better injected in the[illegible] waltzers with [illegible]

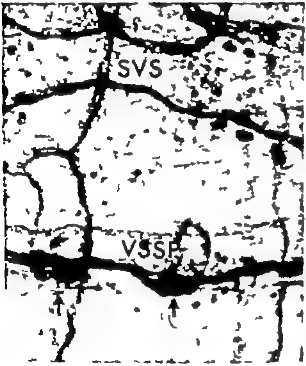

Fig. 8. Waltzing guinea pig, 9?-day-old. A long sec tion of the external wall of the basal turn (above) does not exhibit any changes of the vascular pattern. In high magnification localized areas demonstrate an increased amount of pigment (?), surrounding the vessel of the spiral prominence (*below*). Angiogram, see Fig. 7. *SVS*, stria vascularis. *VSSP*, the vessel of the spiral prominence.

pigment. There was no relation between the changes found in the stria vascularis and in the organ of Corti.

None of these findings could be confirmed in the present strain of the waltzing guinea pig with a dominant mode of inheritance. The capillaries of the stria vascularis appeared normal in all their parts and at all stages of degeneration in the cochlea as compared with healthy controls. The vascular density of the stria vascularis was normal (Table II). The occasional finding, in waltzers and in aged

Table II. *Measurements of the vascular anatomy*

	Normal guinea pig	Waltzing guinea pig
Diameter of VSBM[a] *(µm)*		
Basal turn	5.3	5.7[c]
Second turn	4.7	4.9
Third turn	5.0	4.7
Fourth turn	—	4.9
Diameter of VSTL[b] *(µm)*		
Basal turn	5.5	5.4
Second turn	5.3	5.4
Third turn	5.6	5.2
Fourth turn	—	5.2
Vascular density of the stria vascularis (vessel length/tissue area) (cm/cm^2)		
Basal turn	297.1	308[d]
Second turn	293.6	313
Third turn	300.0	311
Fourth turn	—	297

There are no statistical differences between normal and waltzing guinea pigs.

[a] VSBM = vessel of the basilar membrane (= spiral ... Axelsson, 1968.

[b] VSTL = vessel of the tympanic lip.

[c] Every figure is the mean of 75 measurements (5 measurements in each turn of 15 animals on photographs magnified 150–375).

[d] Every figure is the mean of one measurement in each turn of 15 animals on photographs magnified 150–375

normal guinea pigs, of patchily distributed dense material (pigment?) around the vessel of the spiral prominence might indicate the presence of macrophage activity possibly initiated by absorbed debris from degenerated parts of the cochlea. Small parts of the stria vascularis and of the rest of the cochlea were not well contrast-injected. This is a common finding also in normals and appears to be due more to technical than to anatomical causes. The changes in the stria vascularis evidently do not consist of gross anatomical vascular abnormalities.

In the spiral lamina it is interesting to note that even if the radiating arterioles, supplying the capillary vessels in the close neighbourhood of the organ of Corti, were segmentally uninjected, the spiral capillaries were filled with contrast due to the rich anastomosing possibilities in a spiral direction. The capillaries were not filled with contrast only when several radiating arterioles were uninjected. The apparent dilation of parts of the vessels under the tunnel of Corti and in the tympanic lip was not confirmed by measurements of the diameter of these vessels (Table II). However this does not exclude the possibility that a local severe degeneration of the neuroepithelium could also afflict the elastic elements of vessels in the immediate vicinity. The not infrequent occurrence of granular material, possibly degenerated materia, around the vessel of the basilar membrane and the vessel of the tympanic lip might indicate an absorption at this site.

In conclusion, a complete investigation of all cochlear vessels revealed that the vascular anatomy appears normal in the waltzing guinea pig cochlea in spite of severe degeneration of the organ of Corti. The absence of protein deposition, as a result of cellular degeneration, further indicates that the cochlear circulation is essentially normal in these animals. These findings support the view that the genetic defect in this strain of the waltzing guinea pig does not exert its effect through a deficiency of the vessels.

ZUSAMMENFASSUNG

Die Gefässanatomie der Cochlea des walzenden Meerschweinchens aus einem Stamm mit dominanter Erblichkeit wurde untersucht. Frühere Untersuchungen zeigten eine fortschreitende Degeneration der Haarzellen mit Beginn bei Geburt, sodass dem Cortischen Organ im Alter von sechs bis acht Wochen die Haarzellen praktisch total fehlten. Die Gefässe wurden mit Hilfe von Kontrastmittelinjektion und einer Oberflächen-Präparations-Methode dargestellt. Alle Gefässe der Cochlea wurden in allen vier Windungen untersucht. Die Länge der Gefässe pro Area Gewebe und deren Diameter wurden zwecks statistischer Auswertung gemessen. Abnormalitäten des Gefässystems wurden nicht gefunden, obwohl das ganze Cortische Organ in gewissen Fällen degenerierte. Diese Befunde unterstützen die Ansicht, dass der genetische Defekt von diesem Stamme des walzenden Meerschweinchens nicht seinen Effekt einem Mangel an Gefässen verdankt.

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ELEKTRONEN UND LICHTMIKROSKOPISCHE UNTERSUCHUNGEN ZUR DARSTELLUNG DER GLYKOKALYX IM BEREICH DES DUCTUS COCHLEARIS DES MEERSCHWEINCHENS

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(Eingegangen am 12. Juni, 1971)

Abstrakt. Es wird die Glykokalyx (cell coat), eine dem Plasmalemm außen aufliegende Kohlenhydratschicht, an den Sinnes- und Stützzellelementen des Corti Organs und den angrenzenden Zellformationen des Ductus cochlearis des Meerschweinchens histochemisch und ultrahistochemisch dargestellt. Im Glykokalyxbereich finden sich saure Mukosubstanzen, deren Nachweis durch Eisenbindungsreaktion mit dem Ferrisol nach Krecke erfolgt. Die Glykokalyx ist an allen freien Oberflächen des Sinnes- und Stützepithels des Corti Organs regelmäßig erkennbar. Keine positive Eisenbindungsreaktion findet sich an den Zonulae occludentes sowie zwischen den zellverbindenden Strukturen der Lamina reticularis. Quantitative Unterschiede in der Ausbildung der Glykokalyx sind bei unserem methodischen Vorgehen nicht sicher nachweisbar.

Als Glykokalyx (cell coat) bezeichnen wir eine Zellhülle, die der Außenlamelle des Plasmalemms aufliegt und aus Kohlenhydraten besteht. Sie ist bisher bei zahlreichen Zellarten nachgewiesen. Der Grad ihrer Ausbildung kann wechseln (Geyer et al. 1969; Groniowski et al., 1969; Monis et al., 1969; Nolte & Ohkuma, 1969). Histochemisch bzw. ultrahistochemisch lassen sich mit Hilfe der Eisenbindungsreaktion im Glykokalyxbereich vorliegend saure Mukosubstanzen nachweisen. Die eisenbindende Mukosubstanz ist sialidaselabil und durch Methylierung blockierbar (Bennedetti & Emmelot, 1967; Geyer & Wätzig, 1969). Die Glykokalyx besitzt die Fähigkeit der Ionenbindung, die bisher für Natrium und Chloridionen ultrahistochemisch nachgewiesen ist (Geyer et al., 1969).

Ziel der vorliegenden Untersuchungen ist die Darstellung der Glykokalyx an den Sinnes- und Stützzellelementen des Corti-Organs sowie den angrenzenden Zellformationen im Bereich des Ductus cochlearis.

MATERIAL UND METHODE

Die Untersuchungen wurden an 10 gesunden Meerschweinchen durchgeführt (Durchschnittsgewicht 350 g). In Urethan-Äther narkose erfolgte die Freilegung und Eröffnung der Bulla tympanica. Nach Darstellung des runden Fensters und Anlegung eines feinen Bohrloches an der Apex cochleae entfernten wir den Steigbügel sowie die Membran des runden Fensters. Es wurde ein feiner Polyvinylschlauch in die Öffnung des runden Fensters eingebracht und für fünf Minuten eine intravitale Perfusionsfixierung mit einem 0,1 M phosphatgepuffertem Gemisch von 1,25% Glutaraldehyd und 1,5% Formaldehyd, pH 7,3, durchgeführt. Danach töteten wir die Tiere und fixierten die entnommene knöcherne Schnecke für jeweils weitere vier Stunden in gleicher Lösung.

Die für lichtmikroskopische Untersuchun vorgesehenen Cochleae von fünf Tiere

Acta

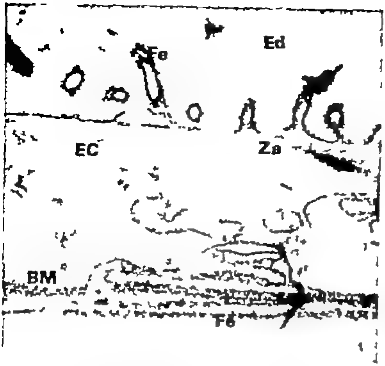

Abb 1 Reissnersche Membran. Gut ausgebildeter Ferrisolpartikelsaum am Plasmalemm der dem Endo- und Perilymphraum zugewandten Zellen. *Fe* Ferrisolpartikel. *BM* Basalmembran. *EC* Epithelzelle. *Za* Zonula adhaerens. *Ed* Endolymphraum. 11 000/30 000 Unkontrastiert.

den in gepufferter gesättigter Chelaplex-Lösung entkalkt und anschließend in Oxydwachs-Methylmetacrylat eingebettet.

Das zur elektronenmikroskopischen Bearbeitung bestimmte Material entkalkten wir nach Abschluß der Fixierung zum Teil in einer phosphatgepufferten 0 1 EDTA Lösung mit Aldehydzusatz (Baird et al., 1967), zum Teil führten wir sofort die vorgesehene Eisenbindungsreaktion durch.

Die Eisenbindungsreaktion erfolgte mit dem ...sol nach Krecke (Methodische Angaben bei Geyer & Wätzig, 1969 und Geyer 1969) Es wurde dabei die gesamte Cochlea inkubiert Die knöcherne Kapsel der Schnecke entfernten wir partiell unter dem Präparationsmikroskop im Bereich sämtlicher Windungen in der Form daß die reagierenden Medien ausreichend freien Zutritt zu den interessierenden Weichteilen hatten. Nachfixierung mit 1%iger Osmiumlösung. Ein Teil der Ultradünnschnitte kontrastierten wir mit Bleicitrat nach Reynolds.

Für die lichtmikroskopischen Untersuchungen führten wir die Eisenbindungsreaktion an Oxydwachs-Methylmetacrylatschnitten durch.

ERGEBNISSE

Die lichtmikroskopischen Untersuchungen nach Eisenbindungsreaktion ergaben bei Lupenvergrößerung eine deutliche Blaufärbung der sauren Mukosubstanzen der Membrana tectoria, der tympanalen Belegzellschicht und des Ligamentum spirale. Auch die Reissnersche Membran zeigte eine gut erkennbare Blaufärbung Die Stria vascularis hebt sich als auffallend heller Streifen deutlich von dem stark blau angefärbtem Ligamentum spirale ab Bei stärkerer Vergrößerung wird an der dem Endolymphraum zugewandten Oberfläche der Stria vascularis ein haarfeiner blauer Saum erkennbar Eine ähnlich zarte Schicht von saurer Mukosubstanz überzieht die epitheliale Oberfläche des Sulcus internus sowie die Lamina reticularis einschließlich der einbezogenen Sinnes- und Stützzellanteile und das Epithel des Sulcus internus. Dieser in seiner Intensität gleichförmige Saum erfährt lediglich in Höhe der Hensenschen eine deutlich stärkere Anfärbung.

Die elektronenmikroskopische Betrachtung bestätigt und erweitert diese Befunde. Die Reissnersche Membran zeigt eine positive

Eisenbindungsreaktion an den freien Oberflächen der Bindegewebszellschicht. Der Basalmembran liegt beiderseits ein Saum von Ferrisolpartikeln an, der sich kontinuierlich auf das laterale und apikale Plasmalemm der beiderseits anliegenden Zellen fortsetzt. Die Oberfläche der Endothelzellen bindet über größere Strecken eine einfache Schicht von Eisenkörnchen, die im Bereich der zahlreichen Mikrovili stärker ausgebildet erscheint. Lediglich im Bereich der Zonulae occludentes fehlt die Eisenbindung (Abb. 1).

Eine kontinuierliche Schicht von Ferrisol-Partikel überzieht die dem Endolymphraum zugewandte freie Oberfläche von Stria vascularis und Ligamentum spirale.

In gleicher Intensität säumen Eisenkörnchen die freien Oberflächen des Epithels des Sulcus externus und der Claudiusschen Zellen. Die zahlreichen zum Endolymphraum gerichteten Mikrovili der Hensenzellen führen zu einer erheblichen Oberflächenvergrößerung mit entsprechend vermehrter Anlagerung von Ferrisol-Teilchen pro μm^2 (Abb. 2). Das Plasmalemm der Deiterschen Zellen zeigt einen eisenpositiven Saum. In den Randzonen sind diesen Stützzellen äußere Spiralfasern dicht angelagert und zum Teil vom Zytoplasma derselben umflossen.

Die Glykokalyx der Nervenfasern und des Plasmalemms der Deiterschen Zellen nähern sich einander hier sehr stark, sind aber noch als zwei getrennte Schichten zu erkennen. An den äußeren und inneren Haarzellen sind Stereocilien und Kutikularplatte von einem mehrschichtigen Saum von Ferrisolpartikel überzogen (Abb. 4, 5). Letzterer ist auch an den von Corti-Lymphe umspülten übrigen Abschnitten der Sinneszellwände nachweisbar. Da auch die an die Sinneszellen herantretenden afferenten und efferenten Nervenendigungen eine gutausgebildete Glykokalyx besitzen, entstehen im Bereich der Synapsen umschriebene dreischichtige Ferrisolsäume mit einem schmalen nichtreaktivem Zwischenraum (Abb. 6). Innere und äußere Pfeilerzellen sowie die den Corti-Tunnel und den Nuelschen Raum durchziehenden Spiralfaserbündel und Basilarfasern und zeigen an ihren freien Oberflächen regelmäßig eine eisen-positive Zone (Abb. 3). Die Eisenbindungsreaktion an den inneren Saumzellen entspricht den Verhältnissen am Epithel des Sulcus externus. Die Membrana tectoria wird *von einem geschlossenen Ferrisolmantel* umgeben.

Abb. 2 Hensenzelle mit positiver Eisenbindungsreaktion an der freien Oberfläche. *Za*: Zonula adhaerens. *M*: Mikrovili. *Fe*: Ferrisolpartikel. 10 000/30 000. Kontrastierung mit Bleicitrat.

Keine Eisenbindung ist an den Zonulae occludentes sowie den ähnlich gestalteten zellverbindenden Strukturen, welche in ihrer Gesamtheit die Lamina vascularis bilden helfen, nachweisbar.

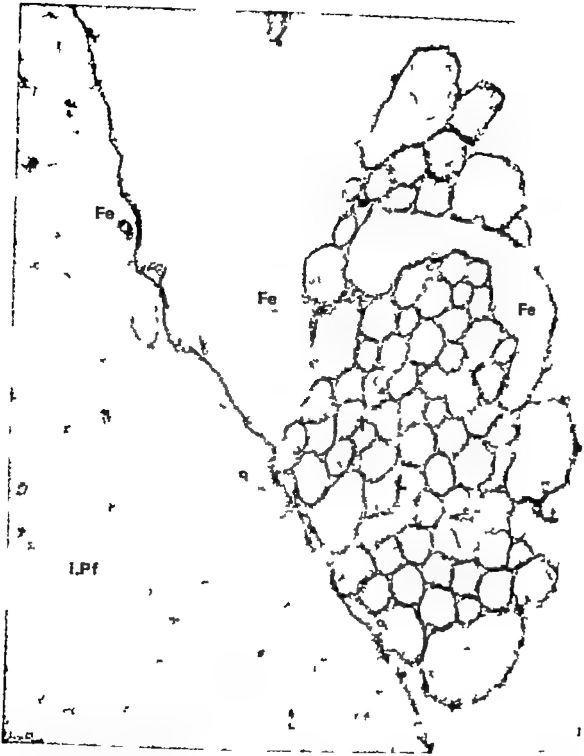

Abb 3 Fasern des Tunnelspiralbündels und Plasmalemm der angrenzenden inneren Pfeilerzelle zeigen einen geschlossenen Überzug von Eisenpartikeln. *T* Tunnelspiralbündel. *I. Pf* innere Pfeilerzelle 40 000. Kontrastierung mit Bleicitrat.

Abb. 4. Äußere Haarzelle. Ferrisolschicht (*Fe*) an der Plasmamembran der Stereocilien und der Kutikularplatte. 15 000/40 000. Kontrastierung mit Bleicitrat.

Auffallend gut ausgebildet ist die Glykokalyx an den tympanalen Belegzellen und deren zahlreichen Zytoplasmaausläufern.

DISKUSSION

Die vorliegenden Untersuchungen lassen eine konstante Ausbildung der Glykokalyx am Plasmalemm aller den reagierenden Medien zugänglichen freien Zelloberflächen im Bereich des Ductus cochlearis erkennen. Die Intensität des Ferrisolpartikelsaumes zeigt nach unseren bisherigen, rein qualitativen Abschätzungen an den verschiedenen Zellformationen keine auffallenden Unterschiede. Die lichtmikroskopisch stärkere Eisenbindungsreaktion im Kopfbereich der Hensenzellen und die der tympanalen Belegzellschicht ist

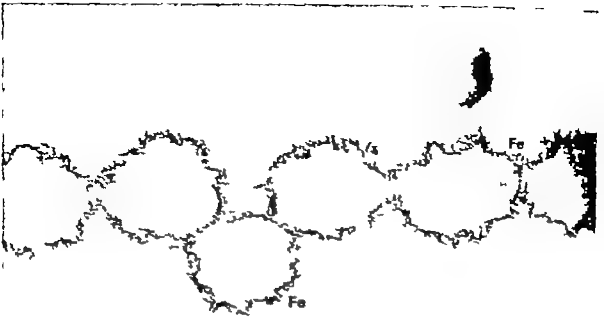

Abb. 5. Stereocilien (Horizontalschnitt) mit gut ausgebildetem Ferrisolsaum (*Fe*). ×9 000/30 000. Unkontrastiert.

nach den elektronenoptischen Befunden durch eine Konzentrierung von Ferrisolpartikeln und damit entsprechend stärkerer lichtmikroskopischer Berliner Blau Reaktion zu erklären. Die vermehrte Ausbildung von Mikrovili an den Hensenzellen sowie die zahlreichen labyrinthähnlich verschlungenen Zytoplasmafortsätze der tympanalen Belegzellen bedingen eine erhebliche Oberflächenvergrößerung mit Bindung von entsprechend mehr Eisenpartikel pro Flächeneinheit. Eine zuverlässige quantitative Auswertung ist u. E. bei der verwendeten Methodik noch nicht möglich. Hierzu müßte die Eisenbindungsreaktion am Ultradünnschnitt oder am 40–60 μ dicken Gefrierschnitt erfolgen, um überall gleichgünstige Diffusionsbedingungen für die reagierenden Medien zu haben.

Für die fehlende Eisenbindung an den Zonulae occludentes sowie zwischen den zellverbindenden Strukturen der Lamina reticularis sind zwei Erklärungen möglich. Es könnten die eisenbindenden Kohlenhydrate in diesen Abschnitten fehlen, oder aber sie sind vorhanden und werden nur aus methodische Gründen von den reagierenden Medien nic erreicht. Die Glykokalyx ist als ein hoc hydratisiertes Gel anzusehen. Ihre Ausdehnu kann in Abhängigkeit vom umgebenden Mi wechseln (Geyer et al., 1969). Ultrahistoch misch konnte ihre Fähigkeit zur Bindung v Natrium- und Chlorionen nachgewiesen w den (Geyer et al. 1969). Es ist nach d Befunden anzunehmen, daß die Glykoka neben elektronegativen sauren Gruppen au basische Gruppen besitzen muß, die als B ungsorte für entsprechende Kationen in Fra kommen. Der histochemische Nachweis le terer steht allerdings noch aus.

Die Natriumionenlokalisation im Berei des Cortischen Organs wurde von Vasil & Kolchev (1969) ultrahistochemisch un sucht. Sie fanden dabei die stärkste Natri ionenkonzentration an der Plasmamem der Stereocilien. Nach Lärmexposition w eine deutliche Verstärkung der Natriu dung im gleichen Bereich festzustellen. Es e scheint nur nach unseren Ergebnissen w

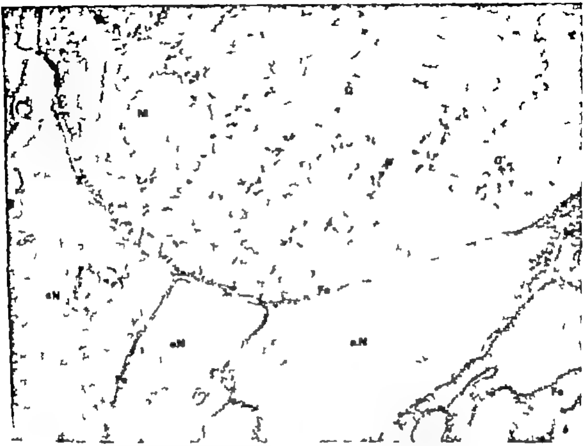

Abb. 6 Basaler Pol einer äußeren Haarzelle. Plasmalemm der Nervenendigungen und der äußeren Haarzelle zeigen eine intensive Eisenbindung. *Fe* Ferribolpartikel. *a.N* afferente Nervenendigung. *e.N* efferente Nervenendigung. *Z.* subsynaptische Zisterne. *M* Mitochondrien. *G* Glykogen. 15 000/75 000. Kontrastierung mit Bleicitrat.

cheinlich daß die sauren Gruppen der Glykokalyx bei den genannten Natriumbindungen zumindest eine wesentliche Rolle spielen.

Die Fähigkeit der Glykokalyx zur Ionenbindung läßt an die Möglichkeit der Beeinflussung des Ionenmilieus an der Zelloberfläche denken. An den Zellformationen des Ductus cochlearis, speziell des Cortischen Organs, in dem wechselnden Ionenmilieu der Endo- und Peri- bzw Cortilymphe könnte dies für die Zellphysiologie bedeutungsvoll sein.

SUMMARY

The article describes a histochemical and ultrahistochemical method for studying the glycocalyx (cell coat), a carbohydrate layer resting on the external surface of the plasmalemm, at the sensory and supporting epithelia of the organ of Corti and the adjacent cell formations of the cochlear duct of the guinea-pig. The method revealed acid mucosubstances in the glycocalyx, which were demonstrated by means of iron-binding reactions with ferribol, according to Krecke. The glycocalyx can be seen regularly at all free surfaces of the sensory and supporting epithelia of the organ of Corti. No positive iron-binding reaction takes place at the zonulae occludentes and between the cell-connecting structures of the lamina reticularis. Quantitative differences in the structure of the glycocalyx cannot be definitely demonstrated with this approach.

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INDIRECT DETERMINATION OF GAS ABSORPTION FROM THE MIDDLE EAR

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Abstract. The absorption of oxygen and nitrogen from the middle ear cavity to the surrounding tissues has been studied quantitatively and 24-hour values have been calculated for subjects with normal ears and intact tympanic membranes. The studies have been ..de according to a method described earlier where ..he central principle is a recording of the volume deviation of the tympanic membrane at changing pres..ure conditions in the middle ear caused by absorption of the respiratory gases. The investigation is limited to persons with a perfect tubal function. The normal absorption of N and O_2/hour and /24 hours has been calculated as well as the corresponding pres.. drop in the middle ear

..osure of normally airfilled cavities often ..r in ear and nose conditions. In the case .. closure of the middle ear changing gas ..tions occur relatively soon and we get .. clinical picture of otosalpingitis or serous .. All the components of the enclosed air ..O_2, N_2 and CO_2, will then be absorbed. If the .. is not closed" and the Eustachian tube .. normally the middle ear can be re.. .. as an intermittently open, non-venti..d gas pocket according to Rahn (1963) In .. case CO_2 will be in equilibrium with the ..rrounding tissues, and only N_2 and O_2 will .. absorbed from the cavity The rate of this ..rocess depends on the molecular size and ..olubility of the gas and the partial pressure ..ifference between the closed cavity and the ..rrounding tissues as well as the area across which the gas is absorbed and the thickness of the tissue through which it diffuses.

Studies of the absorption of air N_2 O_2 and inert gases like xenon and sulphurhexafluoride, SF_6, have mainly been made on animals and elastic, subcutaneous gaspockets have been used. The situation in the middle ear is not equivalent, however as the middle ear constitutes a nearly rigid chamber The absorption of the respiratory gases causes an increasing underpressure if the closure is allowed to remain long enough, all air will be absorbed and replaced by a transudate The volume of the absorbed gas has up till now only been studied after direct contact with the middle ear cavity either by puncture of the intact tympanic membrane and the mastoid cells or through an already existing perforation of the drum. Ingelstedt & Jonson (1967) studied the gas absorption in the middle ear in three cases by direct puncture of the mastoid cells Elner & Nilsén (1970) recorded the biological half time of Xenon^{133} brought to the middle ear by percutaneous puncture of the mastoid cells. Riu et al. (1966) studied the absorption of respiratory gases in cases with a perforated drum and of Xenon^{133} injected through the intact tympanic membrane

We have studied the function of the Eustachian tube in subjects with normal ears (Elner et al., 1971) If the ambient pressure is constant the basic function of the tube is the equilibration of small underpress..

..nvestigation was supported by grants from the ..dish Medical Research Council (B70-14X-99-06 ..d B71-40X-99-07).

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middle ear caused by the continuous absorption of N_2 and O_2

A quantitative evaluation of this absorption is of great clinical value i.e. in connection with different microsurgical procedures in the middle ear. In this paper the gas absorption behind an intact tympanic membrane has been studied with a method described by Elner et al. (1971). This method allows recordings of small volumes and the gas absorption has been determined quantitatively. In this way the absorption for 24 hours can also be calculated, provided that it is uniform during the entire 24 hour period.

Principle of determination

It is possible to determine indirectly and quantitatively the air volume which passes through the Eustachian tube when it opens, ΔV_t, and which replaces the air that has been absorbed from the middle ear to the mucous membranes lining the cavity, ΔV_{diff}. This is done by recording the volume displacement of the tympanic membrane from a retracted position to the neutral position at equilibration of the small underpressures created when the tube is kept closed for 5–10 min. If the middle ear were a completely rigid chamber, the mass of the enclosed gas volume would decrease by ΔV_m and this volume would correspond to the absorbed volume

$$\Delta V_{diff} = \Delta V_m \quad (1)$$

ΔV_m can be calculated according to Boyle's law

$$\Delta V_m = \frac{V_m \cdot \Delta P_m}{(P_{tm} - P_{H_2O})} \quad (2)$$

V_m is the volume of the middle ear and P_{H_2O} is the partial pressure of saturated water vapour at 37 C. The situation in the middle ear however is more complicated. When an underpressure develops the drum is sucked inwards, ΔV_{tm}, and simultaneously the mucous membrane lining the cavity increases its volume, ΔV_{muc} (Fig. 1). These factors counteract the change in the mass of the enclosed gas, ΔV_m, and we therefore get

$$\Delta V_{diff} = \Delta V_m + \Delta V_{tm} + \Delta V_{muc} \quad (3)$$

The absorbed gas volume is replaced by the volume passing through the tube when it opens, and these volumes are identical if the subject can equilibrate his middle ear pressure completely

$$\Delta V_{diff} = \Delta V_t \quad (4)$$

From this it follows that

$$\Delta V_t = \Delta V_m - \Delta V_{tm} - \Delta V_{muc} \quad (5)$$

When the tube opens the drum recoils to its neutral position, the mucous membrane returns to its original volume unless the underpressure has lasted long enough for an oedema to develop, and the change of the mass of the enclosed middle ear gas is eliminated.

METHOD

The essential requirement for calculation of the gas absorption is, that the subject can equilibrate his middle ear pressure completely, i.e. that the tubal function is perfect. First, the middle ear volume is determined according to a method described by Ingelstedt et al. (1967), whereby the calculated volume is corrected for the change of the mucous membrane volume in the middle ear. If this factor is not

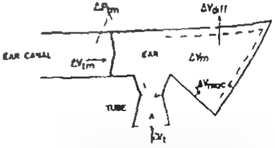


Fig. 1. The different factors influencing the change of volume in the middle ear. ΔV_m, at an underpressure caused by absorption of oxygen and nitrogen. ΔP_{tm} the pressure change across the tympanic membrane

taken into account the calculated volume will be somewhat too great. The calculation is made according to Boyle's law:

$$V_m = \frac{(\Delta V_{tm} - \Delta V_{muc})(P_{atm} - P_{H_2O})}{\Delta P_m} \qquad (6)$$

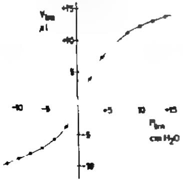
Then the elastic properties of the tympanic membrane system is determined as its volume pressure relationship at small pressure differences across the drum, $V_{tm} = f(P_{tm})$ (Fig. 2)

By this procedure, which has been described earlier (Ingelstedt et al., 1967) all variables can be determined. When the gas in the middle ear is absorbed—and the tube is kept closed—the drum is sucked inwards, i.e. it makes a volume deviation, ΔV_{tm_1}. This volume movement occurs slowly and cannot be accurately recorded. At equilibration, however air passes through the tube and the drum recoils to its neutral position. Hereby a new volume deviation, ΔV_{tm_2} is obtained which can be recorded. It is as great as the volume deviation obtained during the slow absorption phase

$$\Delta V_{tm_1} = \Delta V_{tm_2} \qquad (7)$$

To obtain a volume deviation as great as possible from the neutral position the subject has not been allowed to swallow for 5–10 min

The method for recording the volume deviation of the drum has been described in detail Elner et al. (1971) The essential principle the recording of the air flow in the ear canal



2 The pressure volume relationship of the tympanic membrane system, $V_{tm} = f(P_{tm})$. Neutral position at a.

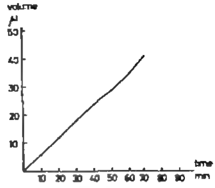


Fig. 3 Recorded curve of gas absorption (Subj. L.A. 240117).

caused by the rapid movement of the tympanic membrane from a retracted position back to its neutral position when air is passing through the Eustachian tube from the rhinopharynx to the middle ear By recording the volume deviation of the tympanic membrane back to its neutral position we can also—indirectly—calculate the pressure change in the middle ear for each period that the tube is closed. This is done with the aid of the volume pressure curve of the tympanic membrane system (Fig. 2) If the ambient pressure is constant, the pressure change in the middle ear is identical with the pressure across the drum (Fig. 1)

$$\Delta P_m = \Delta P_{tm} \qquad (8)$$

As the experiment takes about 90 min the ambient pressure can vary With the aid of an electrical barometer changes in the atmosphere pressure between two equilibrations are therefore continuously recorded and this change is corrected for As a rule it is less than 0.5 mmHg (−0.68 cm H_2O) When the pressure change in the middle ear is known the change of the mass of the enclosed middle ear gas can be calculated according to eq 2. Thereby the tubal ventilation can be determined according to eq 5 The volume change of the mucous membrane is calculated for a mean value of 0.42 µl/cm H_2O (Ingelstedt et al., 1967) By adding the different gas volumes,

Table I *Volume of gas absorbed from the middle ear (1) Recordings from two different occasions (2) Three recordings from two different occasions*

Subject	Middle ear volume (ml)	Volume of gas absorbed/hr (μl)	Volume of gas absorbed/24 hrs (ml)
L. A. 240117	5 9	1) 33 7	0.8
		29 1	0.7
L. A. 390730	4 6	47 4	1 1
E. S. 431129	7.0	29 6	0.7
M F 510717	9.5	32.8	0.8
I J 391226	6.4	2) 33 9	0.8
		25.2	0.7
		28 1	0.7

passing through the tube at each equilibration we get a curve showing the gas diffusion for the period of time covered by the experiment (Fig. 3) Provided that the conditions are identical during an entire 24 hour period the gas exchange can be calculated quantitatively for 24 hours.

MATERIAL

The gas absorption has been studied in 5 subjects with normal ears. Out of these one was examined two and another one three times on different occasions with intervals of several ks (Table I)

RESULTS

Table I shows that the gas absorption from the middle ear to the surrounding tissues is 28 1–47 4 μl/hr (mean value 32 9 μl) The gas volume passing through the tube during 24 hours can be calculated and amounts to 0 7–1 1 ml

DISCUSSION

The method requires a perfect tubal function and only subjects that can equilibrate completely with 1–3 deglutitions (tubal function group Ib, Elner et al., 1971) can be studied for gas diffusion This group includes not quite 40% of subjects with normal ears. The experiments are time-consuming and each subject is studied on at least two occasions since the middle ear volume and the elastic properties of the tympanic membrane system are studied at separate experiments. Table I shows that the values are in good agreement. The subjects have only been allowed to swallow every 5–10 min in order to obtain a volume deviation of the tympanic membrane as great as possible and thereby a more accurate recording To avoid swallowing for a longer period than 10 minutes is very difficult

The diffusion studies have been made in the sitting position We know that owing to changed hydrostatic conditions on the venous side, the tubal function is less good in the recumbent position (Perlman, 1939· Ingelstedt et al., 1967 Rundcrantz, 1969). The mucous membranes lining the middle ear cavity and the mastoid cells will thereby also be affected. It may therefore be assumed that the gas absorption in the middle ear can be slightly changed in the recumbent position which may possibly affect the 24-hour values calculated in this work Though studies in the recumbent position are naturally of great interest they have been impossible to perform since the tubal function is impaired in this position and the recordings would be less accurate. When determining the middle ear volume the change of the mucous membrane volume at an underpressure in the ear must be taken into account If not, the middle ear volume will be somewhat too great and the error is about 7% at a middle ear volume of medium size (6 ml). With respect to the middle ear volumes of the subjects studied here (9.5–4 6 ml) the error should be 4 4–9 1 Thus, the error affects the volume calculations more at small than at large middle ear volumes. Also changes in the ambient pressure during the experiment affects the accuracy of the calculations. In no case however have atmosphere pressure changes exceeded 0.3 mmHg (0 4 cm H_2O). These small changes affect the calculations only slightly and have therefore been disregarded Greater changes in the atmosphere

pressure can, however be of importance because ΔP_m then deviates from the ΔP_{tm}. Also changes in the surrounding temperature can affect the determinations. No such variations have been recorded. The 24-hour values calculated here are somewhat lower than those published by Ingelstedt & Jonson (1967) This latter study was, however made after direct puncture of the mastoid cells and the somewhat higher values can perhaps be explained by reactive hyperemia in the ear caused by the puncture

Since the middle ear volumes of the subjects are known and the absorbed volume of gas per unit of time can be recorded, the resulting underpressure in the middle ear cavity can also be calculated In the subjects examined here the underpressure amounts to 2.8–6 4 cm H_2O/hour (ear volumes of 9.5–4.6 ml) By the fact that the total volume of absorbed gas is known the volumes of nitrogen and oxygen can also be calculated in absolute figures. If the air in the ear may be assumed to have the same composition as expired air it contains about 80% N_2, 15 % O_2 and 5% CO_2. The gas mixture absorbed from the ear cavity to the surrounding tissues will thus consist of 80/95 N_2 and 15/95 O_2. If the total volume for 24 hours is about 0.5–1.0 ml, 0 42–0.84 ml will be nitrogen and 0.08–0 16 ml oxygen. If we calculate with values of N_2 and O_2 according Riu et al. (1966) we get 85/95 N_2 and 10/ O_2 or 0 45–0.9 ml N_2 and 0 05–0 1 ml O_2 the composition of gas in the middle ear to be relatively constant (Melvill Jones, 1961 Riu et al., 1966) and nearly identi- with gas composition in experimental gas (Rahn & Canfield, 1955), the opening the tube will not give a measurable change of this composition and the tube functions or less as a pressure regulator

In a comprehensive work about the physio- of the Eustachian tube from the basis of rption studies of oxygen, Riu et al. (1966) a gas diffusion of 0.553 10^{-3} ml/ n. (N_2+O_2) for a middle ear volume of 4 ml. his would correspond to an underpressure of 0 1 mmHg/min and to an air volume of 0.8 ml for 24 hours. Riu et al. got their values from recording the pressure drop in the ear cavity and calculated the corresponding volumes of nitrogen and oxygen. These values are thus identical with those presented in this work in spite of different technique and method

It has been discussed if the gas absorption in the middle ear is uniform in the mastoid cells and the tympanic cavity itself Tumarkin (1957) and Flisberg et al. (1963) suggested, that the greater part is absorbed in the tympanic cavity where the mucous membrane is more vascularized. A morphological support for this assumption is found in textbooks of anatomy where it is pointed out that "the mucosa of the mastoid cells is poorer in blood vessels" (Rauber Kopsch, 1955) There is no correlation between the middle ear volume and the absorbed gas volume in the subjects studied in this paper The number however is too small to allow any conclusions. Elner & Nilsén (1970) have studied the biological half time of Xenon[133] deposited in the mastoid cells in 9 cases. However no correlation between the volume of the middle ear and the gas absorption was found.

There is a possibility that gas might be exchanged across the normal tympanic membrane and that the values obtained by summation of the single gas portions passing through the tube do not correspond to the real gas absorption across the mucous membrane. Studies with Xenon[133] by Riu et al. (1966) do not support the theory of any appreciable diffusion across the tympanic membrane Elner (1970) studied the diffusion of CO_2 through the tympanic membrane in vitro in a diffusion chamber and—after calculation of the volumes of N_2 and O_2 that could pass through—found that the diffusion only amounts to about 0.5–1 0‰ of the volume passing through the Eustachian tube during 24 hours in vivo Applied to the figures in this study it would be 1–2‰ This figure is probably even lower in vivo as the capillary bed of the tympanic membrane will probably recover part of the

metaplasia (Friedmann 1963) (4) The mucus production by the normal mucous glands in the pharyngeal part of the tube and by the goblet cells may be activated.

Previously an increased number of the goblet cells in the Eustachian tube has been found by Zöllner (1942), in sections from a patient in the healing stage of acute otitis and by Aschan (1954) in two patients with mild otosalpingitis. However there have been no quantitative studies on the density and distribution of goblet cells under normal or abnormal conditions. In acute catarrhal infection of the tube Farrior (1943) found increased mucin in the goblet cells.

On cessation of the pathological stimulus, e.g after healing of acute otitis, the middle ear may often return to normal without the slightest change in the drum, ossicles or mucous membrane In such cases, there is no proof whether the tubal and middle-ear mucosa have been exposed to actions that might have altered the density pattern of the goblet cells. If the pathological stimulus has resulted in the formation of mucous glands, it is possible to obtain, by means of quantitative studies of the glands, a criterion of a previous pathological change of the mucosa. he glands probably do not disappear after e stimulus has ceased, but they may change in shape and function, and the active glands may degenerate (Tos & Bak Pedersen, 1971). On this basis, we carried out in the present material quantitative studies of the mucous glands in the middle ear and osseous tube, obtaining in this way a criterion of previous pathological action upon the mucosa The number of glands was related to the goblet-cell density and goblet-cell pattern in the Eustachian tube

MATERIAL AND METHODS

The material comprises 14 Eustachian tubes and middle ears from 7 males and 7 females. Most of the patients had died of metastasizing cancer At autopsy no acute or chronic diseases of the lower respiratory tract could be demonstrated. The upper respiratory tract was not investigated at autopsy Two patients (cases 3 and 11) had a history of one attack of otitis during childhood. One patient (case 14) had a history of middle-ear catarrh in childhood and thereafter frequent periodical hearing impairment during colds. This patient exhibited mild chronic, secretory otitis. The occurrence, density shape and distribution of the mucous glands in the middle ear of this patient have previously been reported (Bak Pedersen & Tos, 1971 *a*)

At preliminary fixation 2–4 hours after death and at subsequent preparation of the mucosa, the drums were found to be normal in all but 2 patients (Table I) who showed a depressed, atrophic area. The middle-ear mucosa was normal in all but two cases in which it was moderately thickened. The ossicles were normal and mobile in all cases. In all patients but three (Table I) there were adhesions in the antrum, either in the form of membranes, mucosal duplication, or net-formed Three patients had adhesions in the tympanic cavity

The method has been described previously and will merely be summarized here. After fixation the entire tubal mucosa and the mucosa from the entire middle ear were dissected *in toto* removed, and stained by the PAS-alcian blue whole-mount method. The preparations were placed in a chamber filled with anise oil – colophonium and sealed with paraffin. The goblet cells were mounted on a projection screen in the magnification ×500, corresponding to 0 01768 mm² of the epithelium The tube was divided into quarters (first or pharyngeal, second, third, and fourth or tympanic quarter) and into the pharyngeal and tympanic orifice. In each quarter and in the orifices, the goblet cells were counted in six localities, three in the medial and three in the lateral wall. The medial as well as the lateral wall were divided longitudinally into three parts, upper middle and lower third In each locality counts were made in 10 counting

Table I *Findings in the middle ear number and density of mucous glands and mean density of goblet cells in the normal (cases 1–6 and 8) and slightly abnormal series (cases 7 and 9–14)*

	Middle ear findings		Mucous glands			Goblet cells density	
Case no.	Tympanic cavity	Adhesions in the antrum	Number total/active	Middle ear area (mm²)	Density glands/mm²	Tympanic half (3rd + 4th quarter)	Tympanic orifice
1	–	–	9/0	68	0.13	46	3
2	–	–	1/0	246	0.00	77	26
3	–	+	26/0	166	0.16	42	1
4	–	+	2/0	432	0.00	75	19
5	–	+	41/0	100	0.41	58	9
6	–	–	0/0	429	0.00	75	28
8	–	+	12/0	588	0.02	51	8
Mean values			13/0	290	0.04	62	13
7	Scar in the flaccida	+	54/17	168	0.28	82	31
9	Scar in the tensa	+	58/11	259	0.21	132	59
10	Adh. around stapes	+	273/1	150	1.82	83	26
11		+ +	111/33	201	0.55	120	36
12	Adh. to the promontory thick mucosa	+	91/0	297	0.31	92	47
13	Adh. around incus	+	337/2	237	1.42	100	24
14	Thick mucosa	+	444/144	270	1.72	112	110
Mean values			193/30	226	0.85	103	48

fields. In removing the temporal bone it proved impossible in a few of the cases to include the pharyngeal part of the tube. In 6 tubes all localities were represented, and the results are based upon counts of 360 counting fields. In three tubes (nos. 11, 12, and 14) the entire pharyngeal half was missing, and in these cases the results are based upon counts in 180 counting fields. In all, counts were made in 4140 counting fields. The goblet-cell density in the pharyngeal part of 10 tubes (nos. 1–10) was determined previously. Emphasis was laid on changes in the density in the osseous tube and in the tubal orifice as compared with the number of glands in the middle ear. These factors were investigated in all preparations.

Counting of the glands was performed under the stereomicroscope in a magnification of ×40 on the entire mucosa and separately for the different parts of the middle ear. The area of the examined pieces of mucosa was measured and the density calculated.

RESULTS

With a view to the number of mucous glands the material was divided into two series, designated for practical reasons normal when there were less than 50 glands and slightly abnormal when the gland count in the middle ear exceeded 50 (Table I). The mean goblet cell density for each of the two series was calculated.

Mucous glands in the middle ear

The glands were found to be tubular consisting of one or more tubules without acini. By shape and size the glands were divided into (*a*) simple tubules without branchings, (*b*) branched glands with two tubules, (*c*) branched glands with four tubules, and (*d*) larger glands with several tubules (Fig. 1). In the normal as well as in the abnormal series simple tubules predominated. However, preparations with many glands (Table I) contained a number of

Fig. 1. (A) Two large branched, active glands with several tubules. (B) One large degenerated gland and several small glands. Whole mount, 160

branched glands with two tubules and a few larger glands. Previously three secretory stages of the glands have been described. Active glands with secretory epithelium (Fig. 1 a), degenerated glands in which the secretory epithelium was replaced by simple or stratified PAS-alcian blue-negative epithelium (Fig. 1 b) well as transitional forms between the two & Bak-Pedersen, 1971).

In the normal series all glands were degenerate and there were no active glands (Table I). In the slightly abnormal series there was also a predominance of degenerate glands but in addition there were active glands, mainly in the tympanic orifice. On preparation 14 there were quite a number of active glands and small amounts of mucus on the surface of the middle-ear mucosa. Predominance of degenerate glands presumably indicates that the glands were laid down a very long time ago, that the process which has caused their formation has long ago ceased, and that the middle ear is again clinically healthy.

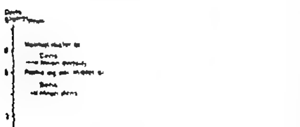
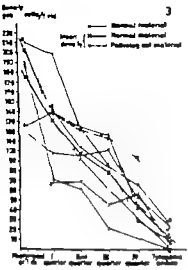


Fig. 2. Density of glands in various localities of the middle ear in the normal and slightly abnormal series.

The normal series (Table I) exhibited in the entire middle ear an average of 13 glands with a mean density of 0.04 glands per mm². In most cases glands were found in only a few parts of the middle ear, at most in three of the 11 areas examined. The density of glands in the individual areas was low (Fig. 2).

In the abnormal series (Table I) there was an average of 193 glands with a mean density of 0.85 glands per mm². The gland count ranged from 54 to 424. The glands were present in nearly all parts of the middle ear but the density differed a great deal in the



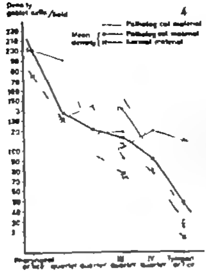


Fig 3 Density pattern in the individual Eustachian tubes from the normal series. Mean density in the normal and slightly abnormal series.

Fig 4 Density pattern in the individual tubes from the slightly abnormal series. Mean density in the normal and slightly abnormal series.

different areas (Fig. 2) In a few places, how ever the density might be very high, about 6 glands per mm² The mean density proved highest in the niche of the oval window and on the stapes where all preparations contained glands.

Only two preparations of the abnormal series also exhibited glands in the osseous tube, three glands in preparation 9 and 64 glands in preparation 14 localized mainly in the fourth quarter of the medial wall.

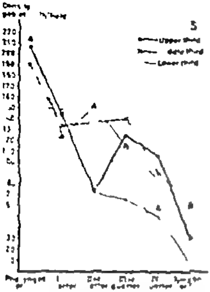
Goblet-cell density and density pattern

The mean goblet-cell density in the tympanic half of the Eustachian tube was considerably lower in the normal series than in the slightly abnormal one. The same applies to the mean density in the tympanic orifice (Table I)

The density pattern in the total normal series (Fig. 3) showed a pronounced and regular decrease of total mean density into the tympanic direction and a very low density in the tympanic orifice The regular decrease in density from quarter to quarter was observed in practically all the tubes, except in those which already showed a relatively low density in the pharyngeal part (nos. 2 and 8)

In the slightly abnormal series (Fig 4) the total mean density proved to be considerably higher than in the normal series in all parts except the first quarter The density pattern in the slightly abnormal series as a whole differed considerably from that in the normal series, showing a very slight decrease in mean density as far as the fourth quarter From the fourth quarter to the tympanic orifice the decrease in density was again marked but still the density in the tympanic orifice was fairly high. Analysis of the density patterns for the individual tubes showed that in most cases the density increased appreciably in one of the quarters, but it fell markedly in the tympanic orifice in all the tubes except one (no 14) in which it was particularly high. This patient had mild secretory otitis with the highest gland count in the middle ear and especially a considerable number of active glands (Table I) Presumably the relation between the number of active glands and the high goblet-cell density in the tympanic orifice is a factor of importance, indicating that the mucous membrane is still fairly secretory In the other cases with a particularly high gland count, but with practically no active glands (nos. 10 and 13) the mean density in the tympanic half as well as in the tympanic orifice was not higher than in cases having a gland count of 50–100, but which contained some active glands.

As has been demonstrated previously there were marked differences in density between



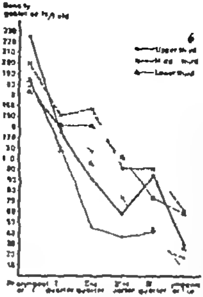


Fig 5 Mean density in the upper middle, and lower thirds of the medial wall in the normal and in the slightly abnormal series, which is indicated by thicker lines.

Fig 6 Mean density in the upper middle, and lower thirds of the lateral wall in the normal and in the slightly abnormal series, which is indicated by thicker lines.

the roof and other parts of the tube especially in the second and third quarters.

In the *medial wall* (Fig 5) the density decreased markedly in the upper third of the tube in the normal as well as abnormal series, so that in the second quarter it was equally low in both. In the third quarter the density increased markedly in the upper third in the slightly abnormal series, whereas in the normal series it was still low The density in the middle and lower thirds of the tube was increased in the slightly abnormal series as compared with the normal series, but the pattern f the decrease in density towards the tym nic direction was approximately the same Thus, during a pathological action there was, apart from a diffuse increase in density in the tympanic part of the tube also a very pronounced increase in density in the upper areas. While in the normal series there were areas in the tubal roof entirely devoid of goblet cells, such areas were uncommon in the slightly abnormal series Thus, during a pathological action there occurs also a spread of goblet cells over a large area

In the *lateral wall* (Fig 6) there was in the abnormal series too a marked increase in density in the upper third, but the increase occurred in the fourth quarter not in the third as in the medial wall. The considerably lower density in the upper third of the tympanic orifice in the medial as well as lateral wall, is not surprising, as these areas border on the epitympanum where goblet cells do not as a rule occur The lower third borders on the hypotympanum and the middle third is the medial wall on the anterior part of the promontory where the slightly abnormal series also showed an increased density of goblet cells. In the lateral wall too the slightly abnormal series exhibited a *diffuse* increase in density in all parts of the tympanic half of the tube but especially in the upper part of the fourth quarter in which the goblet-cell area was extended

DISCUSSION AND CONCLUSION

As already mentioned under Technique, three problems, in particular call for discussion (1) Whether one series of the presented material is normal and the other series slightly abnormal. (2) Whether the mucous glands make up a normal or abnormal component of the middle-ear mucosa. (3) Whether the increased goblet-cell density in the tympanic orifice and in the osseous tube represents marked individual variations in density or a sequel of previous pathological action upon the mucosa.

Re 1 (*a*) *Normal series*. All the patients had

clinically normal middle ears at the time of death. One (case 3) had a history of otitis during childhood. When dissected, the middle ears proved entirely normal except for adhesions in the antrum in 4 cases (Table I) It is difficult to assess whether the isolated adhesions, which were usually in the form of mucosal duplications across the antrum, were a sequel to previous otitis or due to anomaly in the process of pneumatization. Apart from the adhesions in the antrum, the normal series was also normal patho-anatomically although it cannot be ruled out that several of the may previously have had acute otitis or middle-ear catarrh. Even with a very thorough history taking there is never a guarantee that the patients can remember catarrhal or purulent otitis from their early childhood.

(b) *Slightly abnormal series* In this series too there were no manifest acute or chronic middle-ear diseases at the time of death, so that is series too must be considered clinically except for case 14 who had mild chronic secretory otitis. The other patients (Table II) exhibited certain signs of previous acute otitis. Only one (case 11) presented entirely nor appearances of the tympanic cavity This had a history of acute otitis, and in the antrum there were considerably more pro- adhesions than in the others. Patho-anatomically therefore, this series must be ered slightly abnormal, and the middle must previously have been exposed to l stimulus, possibly acute otitis edia.

Re 2. It is a view prevailing among otolo-sts and histologists that no mucous glands re present in the osseous Eustachian tube or the middle ear (Moos, 1874 Politzer 1908 ollner 1942 Graves & Edwards, 1944 Egg & Wolff 1947 Friedmann, 1963 and Such glands have also not been found prematures (Buch & Jørgensen, 1964) or in oetuses (Tos, 1970- Tos, 1971 *a* *b*) Sadé 1966 *a*), studying sections of 80 temporal ones from patients "known to be suffering from non-otologic diseases at the time of death" found "glands here and there beneath the ciliated epithelium of the tympanic cavity in most ears" He gave no further description of the material, neither concerning possible previous otitis nor any other pathological findings in the middle ear As long as systematic studies of the mucosa have not disclosed glands in foetuses and prematures or in children definitely known not to have had diseases of the ear or upper respiratory tract, there is in our opinion still no proof that the glands form a normal component of the mucosa of the osseous tube and middle ear

In our normal series only one patient showed no glands. In all the others glands were present, but in most of the cases in rather small numbers. In the slightly abnormal series several patients had fairly high gland counts, highest in case 14 in whom the pathological changes were also most pronounced and who had a definite history of periodical middle-ear symptoms. In these cases there is no doubt that the glands are abnormal. The findings indicate that glands may occur in an ear which clinically and otherwise patho-anatomically is normal, but they do not prove that such glands form a normal component of the mucosa. It may be imagined that under the influence of a mild pathological action there will occur in a few sites of the middle-ear mucosa, metaplasia with formation of a few glands which thereafter degenerate, but remain in the mucosa. In the event of recurrent stimuli new glands may form. Possibly the stimulus need not be a purulent infection, and possibly a catarrhal state may entail the formation of glands. Animal experiments (Friedmann, 1955 Senturia et al., 1962) have shown that low-virulent infection and long-lasting tubal occlusion causes metaplasia of the middle-ear epithelium into ciliated, pseudostratified columnar epithelium with goblet cells and mucous glands.

In a study as yet unpublished, determining the density of glands by the whole mount method in more than 2 000 biopsies removed

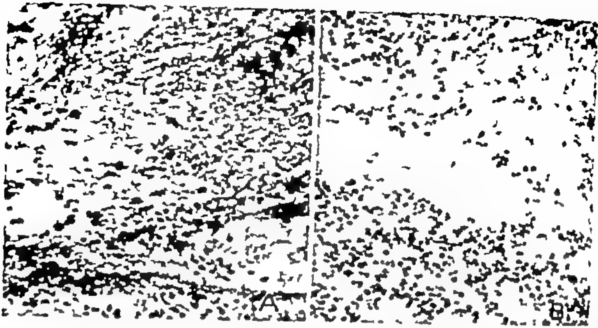


Fig 7 (A) Increased goblet-cell density in the medial wall of the tympanic orifice (case 9). (B) Greatly increased density from the same locality (case 14). The irregular distribution of the goblet cells is evident. Whole mount. ×120.

at operation from the middle ear from various disease groups, we have found in dry ears with sequelae of otitis an extremely varied density ranging from 0 to 10 glands per mm² In chronic suppurative otitis we found in most cases a considerably greater density of glands and in chronic adhesive otitis a very great density from 2 to 15 glands per mm² in a few cases even greater Others (Friedmann, 1963 Bendek 1963 Sadé 1966 *b* Palva et al. 1968 Sadé & Weinberg 1969 De Moura & Hayden, 1969) have previously though not on a quantitative basis, demonstrated mucous glands in chronic middle-ear diseases such as secretory otitis and chronic suppurative otitis media

In other words there is a definite quantitative relationship between the number and density of glands between the normal series with very slight density the slightly abnormal series with greater and yet varying density and the highly abnormal biopsy material with very great density

Re 3 There was a clear difference in mean goblet-cell density in the tympanic half of the tube as well as in the tubal orifice between the normal and the slightly abnormal series indicating that in cases where the number of glands is increased the density of goblet cells is also increased. In case 14 where the number of glands and the number of active glands was highest, the goblet-cell density was also greatest Although the distribution of goblet cells has been found to be irregular (Bak Pedersen & Tos, 1971 *b*), showing marked variation in density within the same counting field and between different neighbouring fields (Fig 7) the density in each quarter represents the mean of 60 counting fields, which must give a real impression of the change in density Therefore, the increase in goblet-cell density can hardly represent a normal individual variation, but must be a sequel to previous pathological actions upon the mucosa Investigations of larger normal and abnormal materials are required to clarify the magnitude of normal variations and changes in density during acute and chronic disease states. An increase in density as a consequence of acute action is presumably reversible since otherwise an enormous increase in density would be expected upon

recurrent actions. In the trachea Ellefsen & Tos (1971) found the goblet-cell density to be only moderately increased in acute and in recurrent tracheobronchitis, while in typical chronic tracheobronchitis it was greatly increased.

ZUSAMMENFASSUNG

Von 14 Felsenbeinen wurde die Schleimhaut des Eustachischen Rohres und des Mittelohres herauspräpariert und mit PAS-Alcianblau im Stück gefärbt. Die Dichte der Becherzellen in den verschiedenen Abschnitten der Tuba wurde auf Grund der 4 110 Zählungen des 0.01768 mm² grossen Zählungsfelder bestimmt. Anzahl und Dichte der Drüsen im ganzen Mittelohr sowie in den verschiedenen Teilen des Mittelohres wurden bestimmt. Bei normalem Material wurden bis zu 50, durchschnittlich doch 13 Drüsen gefunden, mit einer durchschnittlichen Dichte von 0.04 Drüsen/mm². Bei dem leicht pathologischen Material wurden zwischen 50 und 440 Drüsen gefunden, mit einer durchschnittlichen Dichte von 0.85 Drüsen/mm². Die Becherzellendichte in den knöchernen Teilen der Tuba und im Ostium tympanicum war kleiner bei dem normalen als bei dem leicht pathologischen Material. Das Muster der Becherzellendichte zeigte bei dem normalen Material einen starken und regelrechten Fall der Dichte in der tympanalen Richtung und eine sehr kleine Dichte im Ostium tympanicum. Bei dem leicht pathologischen Material gab es einen moderaten Fall der Dichte in der tympanalen Richtung und eine relativ grosse Becherzellendichte im Ostium tympanicum. Die Steigerung der Becherzellendichte bei dem leicht pathologischen Material war am grössten im Dach der Tuba, wo die Dichte unter normalen Verhältnissen klein ist. Die Bildung der Drüsen und Erweiterung der Zonen mit Becherzellen ist wegen früherer pathologischer Einflüsse auf die Schleimhaut eine Folge der Schleimhautmetaplasie im Mittelohr und in der knöchernen Tuba.

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DIRECTIONAL AUDIOMETRY

VI *Directional Speech Audiometry in Patients with Practical Deafness in One Ear and Impaired Hearing in the Other Ear Treated with Hearing Aids*

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(Received December 30, 1971)

Abstract Directional Threshold of Intelligibility (DTI) was investigated in 20 patients with practical deafness in one ear and impaired hearing in the other ear The DTI was measured without and with background noise, without and with hearing aid. All of the patients were examined with a special form of hearing aid. A microphone was placed on each ear and impulses from these were transmitted to the better ear Seven patients were also examined with behind the-ear hearing aid fitted on the better ear The first form of treatment seemed to give better results.

Patients with no usable hearing or deafness in the one ear and impaired hearing in the other ear have formerly been treated with a hearing aid on the better ear Mouzon (1955) placed on both ears microphones and connected them to separate amplifiers which in turn transmitted the impulses to a common telephone Of two methods described by Fowler (1960) one has later been widely used hearing aid was placed on the best ear and an extra microphone placed on the other ear was connected to the amplifier of the hearing aid This method is easy to carry out, as hearing glasses can be used Harford & Barry (1965) and Harford (1967) reported good experience of this type of treatment

The aim of this investigation was to chart how speech comprehension is affected both without and with noise by treatment with a hearing aid with two microphones

METHOD

Throughout the following the dB reference level is 0 0002 dyne per square centimetre. Hearing loss in dB refers to British Standard 2497–1954 The relationship between British Standard and ISO Standard is shown in Table I (Whittle & Delany 1966) The apparatus and method are described in detail by Tonning (1970 1971 *a* and *b* 1972 *a* and *b*). The dB values of DTI (Directional Threshold of Intelligibility definition Tonning, 1971 *a*) was recorded without noise with the signal loudspeaker reproducing speech in four different positions in the horizontal plane (0 = in front, 90 = to the right 180 = behind, and 270 = on the left side of the person tested).

DTI was also determined during simultaneous stimulation with white noise: the signal loudspeaker was placed in each of the previously mentioned four positions in turn. For each of these positions, the noise loudspeaker was placed in the same four positions, resulting in a total of 16 different combinations of positions in noise.

(Statistics in this article: Wilcoxon-Test for paired comparisons, level of significance 0.05. References: Dixon & Massey 1957 Siegel, 1956 Electronic computer was used, the programmes being taken from IBM's System 360

Table I *The relationship between British Standard 1954 and ISO Standard 1964 for our equipment (earphone TDH 39/MX41AR, 9A coupler)*

The table indicates the number of dB that must be added to the threshold of hearing recorded in British Standard when transferring to ISO Standard

Frequency Hz	125	250	500	1 000	2 000	4 000	6 000	8 000
dB added to hearing loss in British Standard when transferring to ISO Standard	+3.5	+3.7	+2.0	2.9	−0.2	0.0	+7.9	+5.5

Scientific Subroutine Package (360A-CM-03X) Version III 1968.)

MATERIAL

Twenty *right handed experimental subjects*, (9 women and 11 men) from 44 to 80 years old (average age 66.4 years, median age 68 years) were examined. Pure tone audiograms were recorded for the frequencies 125 250, 500, 1 000 2 000, 4 000 6 000, and 8 000 Hz, using a Madsen Electronics Audiometer Model OB 60, calibrated according to British Standards.

The patients had severe hearing loss up to deafness in the one ear The other ear had a PTA between 23 and 55 dB hearing level. (PTA, i.e., Pure Tone Average the mean of the hearing levels at the frequencies 500, 1 000, and 2 000 Hz.)

Nine patients (Nos. 3 5 6, 8 9 10, 16, 17 and 20) had used behind-the-ear hearing aids on the better ear before this investigation started.

The patients are listed in Table II.

Before the investigations with hearing glasses with two microphones the 20 patients had used these hearing aids for at least 3 months. Seven patients were also examined with conventional monaural hearing aid on the better ear These aids were likewise used at least 3 months before the tests were made.

All of the 20 patients were tested with hearing glasses resembling those described by Harford & Barry (1965) and Harford (1967). There was a microphone in each templepiece. The impulses from both microphones were transmitted to an amplifier in the templepiece at the better ear From a telephone in the same templepiece sound was transmitted via a tube to the better ear The patients Nos. 1 2, 4 13 and 14 did not use ear-mould, since *during preliminary speech audiometric measurements* better discrimination was obtained in silence and in noise without an ear mould. The patients themselves also found it more pleasant to dispense with the ear-mould. Two types of hearing glasses were employed.

1 *Danavox 620* A microphone of type Danavox 5450-01 was used on the better ear whilst on the other side a Knowles 1451 was used.

2. *Oticon 830S.* This had a Knowles BE 1532 microphone on each side but an aeration of the telephone casing on the side of the poorer ear had been made.

The microphones chosen for the Danavox apparatus and the aeration of the one telephone casing in the Oticon hearing aid gave the frequency of the microphone on the side of the poorer ear a character in which the deeper tones were more pronounced than they were in the other microphone

RESULTS

DTI without noise both without and with hearing aid with two microphones

The mean values of DTI ($\overline{\text{DTI}}$) were calculated for each position of the signal loudspeaker and listed in Table III

It was found that the DTI with hearing aid with two microphones was better than the DTI

Table II *Patients with binaural hearing loss*

PTA: Pure Tone Average. Mean of the hearing levels at 500, 1 000, and 2 000 Hz.
Re: Residual hearing. Hearing not measurable at all frequencies tested.
No: No measurable hearing.
Cond: Conductive hearing loss.
Sn. Sensorineural hearing loss.
Mixed: Combination of conductive and sensorineural hearing loss.

No.	Right ear PTA	Left ear PTA	Type hearing loss in best ear	Sex	Age	Type of hearing aid: 2 microphones	Type of hearing aid: 1 microphone
1	No	27	Sn	♀	74	Danavox 620	
2	No	27	Sn	♂	80	Danavox 620	
3	Re	30	Sn	♀	66	Oticon 830S	Widex 641
4	Re	32	Sn	♀	70	Danavox 620	
5	Re	33	Sn	♂	61	Oticon 830S	Oticon 560S
6	No	35	Sn	♂	53	Danavox 620	
7	Re	37	Sn	♂	65	Danavox 620	Danavox 620
8	No	37	Cond	♀	62	Oticon 830S	Oticon 830S
9	Re	40	Mixed	♀	62	Danavox 620	Danavox 620
10	Re	42	Sn	♀	76	Danavox 620	
11	Re	45	Sn	♂	60	Danavox 620	
12	No	55	Sn	♂	77	Oticon 830S	Oticon 830S
13	[illegible]	Re	Sn	♂	69	Danavox 620	Danavox 620
14	28	No	Sn	♀	70	Danavox 620	
15	35	Re	Sn	♀	67	Danavox 620	
16	42	Re	Sn	♀	70	Oticon 830S	
17	43	No	Sn	♂	77	Oticon 830S	
18	45	No	Sn	♂	45	Oticon 830S	
19	47	Re	Sn	♂	79	Danavox 620	
20	48	No	Sn	♂	44	Danavox 620	

without hearing aid for all the 4 listening conditions (Table III).

DTI in noise both without and with hearing aid with two microphones

For each of the 16 combinations of signal and noise loudspeakers the arithmetic means of the DTI values ($\overline{DTI}$) were calculated both without and with hearing aid (Table IV).

The DTI was significantly improved by the use of hearing aid in 11 of the 16 experimental conditions (Table V). For the other five experimental conditions there was no significant effect on the DTI using the hearing aid with two microphones. It should be added that without a hearing aid the best (lowest) DTI values were found under these five experimental conditions.

The effect of hearing aid on the individual DTI

Each person was examined to find out whether there was a significant difference without and with hearing aid with two microphones in the DTI for the 16 positions with noise (DTI_{n}) and also whether there was a difference without and with hearing aid in the DTI for all the 20 experimental conditions (DTI_{sa}). The 7 patients who had also for a period used monaural

Table III *The influence of azimuth on the aided and unaided DTI in 20 patients with practical deafness in one ear and impaired hearing in the other ear, no background noise, hearing aids with 2 microphones are used*

$\overline{DTI}$: The mean value of DTI for each position of the signal loudspeaker

Position of signal loudspeaker	$\overline{DTI}$ without hearing aid	$\overline{DTI}$ with hearing aid with 2 microphones	Effect of hearing aid with 2 microphones on DTI
In front	49.5	31.2	Improvement
Poorest ear	54.1	31.0	Improvement
Behind	50.5	32.7	Improvement
Best ear	46.9	29.5	Improvement

Table IV *The DTI values (= the arithmetic mean of the DTI values) for the various combinations of signal and noise loudspeakers both without and with the use of hearing aid with two microphones*

Position of signal loudspeaker	DTI without hearing aid	DTI with hearing aid with 2 microphones	DTI without hearing aid	DTI with hearing aid with 2 microphones
	Position of white noise loudspeaker: In front		Position of white noise loudspeaker: Behind	
Front	61.3	57.6	60.0	55.6
Poorest ear	64.1	55.1	63.7	54.4
Behind	61.1	58.2	61.0	57.3
Best ear	57.3	54.9	56.9	53.1
	Position of white noise loudspeaker: Poorest ear		Position of white noise loudspeaker: Best ear	
In front	57.8	57.4	63.6	58.6
Poorest ear	62.1	58.4	67.1	57.6
Behind	59.0	59.2	64.2	59.3
Best ear	55.0	55.7	61.2	57.4

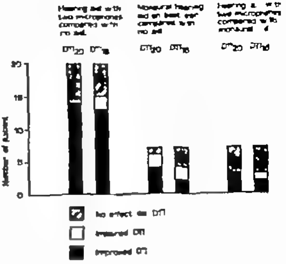

Fig 1 The effect of hearing aids on DTI_{20}. The DTI both without and with background noise (4 loudspeaker positions without, and 16 with background noise). DTI_{16}. The DTI with background noise (16 loudspeaker positions). 20 patients are examined with hearing aid with two microphones. Of these are 7 examined also with monaural conventional head-borne hearing aid on the better ear.

behind-the-ear hearing aid were examined as to whether a statistically significant difference in DTI_{16} and DTI_{20} could be detected with such a hearing aid as compared with no apparatus, and whether there was a difference in the values found with hearing aid with bilateral microphones compared with monaural conventional hearing aid. The results are presented in Fig. 1

Use of the standard diagram

In evaluating the effect of the hearing aid, the standard diagram previously described (Tonning, 1971 *a* and *b* 1972 *a* and *b*) may be used. In Fig. 2 this diagram is used to illustrate how hearing aid can influence the DTI values under various experimental listening conditions for two of our patients.

PATIENT NO 9

1 Without hearing aid, the signal loudspeaker aimed at the left ear the noise loudspeaker aimed at the right ear DTI without noise 46 dB. DTI with noise: 51 dB Point plotted at A.

2. With hearing aid, the same positions of the loudspeakers: DTI without noise: 22 dB. DTI with noise 60 dB Point plotted at B

Table V *The effect of hearing aid with two microphones on the DTI for the 16 various combinations of signal and noise loudspeakers*

Position of signal loudspeaker	Position of the white-noise loudspeaker: In front	Poorest ear	Behind	Best ear
In front	Improvement	No effect	Improvement	Improvement
Poorest ear	Improvement	Improvement	Improvement	Improvement
Behind	Improvement	No effect	Improvement	Improvement
Best ear	No effect	No effect	No effect	Improvement

Table II *Patients with binaural hearing loss*

PTA. Pure Tone Average: Mean of the hearing levels at 500, 1 000, and 2 000 Hz.
Re: Residual hearing. Hearing not measurable at all frequencies tested.
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No.	Right ear PTA	Left ear PTA	Type hearing loss in best ear	Sex	Age	Type of hearing aid: 2 microphones	Type of hearing aid: 1 microphone
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4	Re	32	Sn	♀	70	Danavox 620	
5	Re	33	Sn	♂	61	Oticon 830S	Oticon 560S
6	No	35	Sn	♂	53	Danavox 620	
7	Re	37	Sn	♂	65	Danavox 620	Danavox 620
8	No	37	Cond	♀	62	Oticon 830S	Oticon 830S
9	Re	40	Mixed	♀	62	Danavox 620	Danavox 620
10	Re	42	Sn	♀	76	Danavox 620	
11	Re	45	Sn	♂	60	Danavox 620	
12	No	55	Sn	♂	77	Oticon 830S	Oticon 830S
13	23	Re	Sn	♂	69	Danavox 620	Danavox 620
14	28	No	Sn	♀	70	Danavox 620	
15	35	Re	Sn	♀	67	Danavox 620	
16	42	Re	Sn	♀	70	Oticon 830S	
17	43	No	Sn	♂	77	Oticon 830S	
18	45	No	Sn	♂	45	Oticon 830S	
19	47	Re	Sn	♂	79	Danavox 620	
20	48	No	Sn	♂	44	Danavox 620	

without hearing aid for all the 4 listening conditions (Table III)

DTI in noise both without and with hearing aid with two microphones

For each of the 16 combinations of signal and noise loudspeakers the arithmetic means of the DTI values ($\overline{\mathrm{DTI}}$) were calculated both without and with hearing aid (Table IV)

The DTI was significantly improved by the use of hearing aid in 11 of the 16 experimental conditions (Table V) For the other five experimental conditions there was no significant effect on the DTI using the hearing aid with two microphones. It should be added that without a hearing aid the best (lowest) DTI values were found under these five experimental conditions.

The effect of hearing aid on the individual DTI

Each person was examined to find out whether there was a significant difference without and with hearing aid with two microphones in the DTI for the 16 positions with noise (DTI_{sd}) and also whether there was a difference without and with hearing aid in the DTI for all the 20 experimental conditions (DTI_{sd}). The 7 patients who had also for a period used monaural

Table III *The influence of azimuth on the aided and unaided DTI in 20 patients with practical deafness in one ear and impaired hearing in the other ear: no background noise; hearing aids with 2 microphones are used*

$\overline{\mathrm{DTI}}$ The mean value of DTI for each position of the signal loudspeaker

Position of signal loudspeaker	$\overline{\mathrm{DTI}}$ without hearing aid	$\overline{\mathrm{DTI}}$ with hearing aid with 2 microphones	Effect of hearing aid with 2 microphones on DTI
In front	49.5	31.2	Improvement
Poorest ear	54.1	31.0	Improvement
Behind	50.5	32.7	Improvement
Best ear	46.9	29.5	Improvement

an opinion to be formed about the effect of the treatment

An uncritical application of a head-borne hearing aid with microphones on both sides is not to be recommended. It must not be forgotten that, particularly in noise it may be easier to turn the head into the most favourable hearing position when using the conventional head-borne hearing aid than when using an apparatus with two microphones.

It should however be possible to get an impression of the effect of the hearing aid on the DTI under certain conditions by using the standard diagram. In using the diagram as demonstrated in this paper the deviations in the results of the measurements affects the reliability of the points plotted Provided this is taken into account together with the fact that our experimental listening conditions diverge from conditions met with daily (Tonning, 1971 *b* 1972 *a* and *b*) the standard diagram would be of help in making an evaluation of the effect of the hearing aid treatment.

ZUSAMMENFASSUNG

Die gerichtete Verständlichkeitsschwelle (DTI-Directional Threshold of Intelligibility) wurde bei 20 Patienten mit praktischer Taubheit auf einem Ohr und herabgesetzter Hörfähigkeit auf dem anderen Ohr untersucht. Die DTI wurde sowohl mit als auch ohne Hintergrundgeräusch, mit und ohne Hörgerät gemessen. Sämtliche Patienten wurden mit einer speziellen Form von Hörgeräten untersucht. Mikrophone wurden an beiden Ohren angebracht, und Impulse von diesen wurden an das bessere Ohr übergeleitet. Sieben Patienten wurden ausserdem mit einem hinter dem besseren Ohr angebrachten Hörgerät untersucht. Die erstgenannte Behandlung schien bessere Resultate zu geben.

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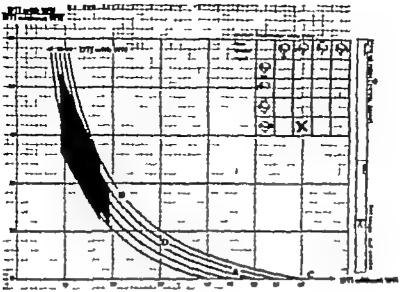

Fig 2 Coordinate system, illustrating the effect of hearing aid under certain conditions. *Abscissa*. DTI without noise *Ordinate* DTI with noise divided by the corresponding DTI without noise i e with the signal loudspeaker in the same position. DTI in noise is also indicated Curved lines. Shaded figure covers the area where 95% of the DTI values of 30 normally hearing listeners are to be plotted (Tonning, 1971 a). DTI values for 2 patients are plotted in the diagram. For further explanation see text.

The location of the points in the coordinate system indicates that in this case and under these experimental conditions hearing aid im proved DTI in silence considerably whilst DTI in noise became worse (In noise without hearing aid the DTI was not worse than the DTI values of the 30 normally hearing per sons.)

PATIENT NO 12

1 Without hearing aid, signal loudspeaker aimed at the left ear noise loudspeaker aimed at the right ear DTI without noise 62 dB DTI with noise 63 dB Point plotted at C

2 With hearing aid, the loudspeakers in the same positions: DTI without noise. 31 dB DTI with noise 54 dB Point plotted at D

The location of point C and D in the coordinate system indicates that DTI in silence was improved with a hearing aid, but was not so good as the 30 normal hearers DTI values. In noise the hearing aid improved speech comprehension so much that the DTI values found did not differ from the DTI values of the normal hearers.

COMMENTS

With otological examination of patients and consideration of their audiograms alone, the effect of one rather than another form of hearing aid treatment could not be determined in advance Nor could the patients own comments in the process of becoming adapted to the hearing aid always be regarded as reliable.

At the present stage the only possibility of deciding which form of hearing aid treatment should be chosen seems to be to evaluate first the patient s need to receive informative acoustic impulses under different every day conditions. After the patient has tried out the hearing aid over a period of time, discussion with and examination of the patient will allow

an opinion to be formed about the effect of the treatment.

An uncritical application of a head-borne hearing aid with microphones on both sides is not to be recommended. It must not be forgotten that, particularly in noise, it may be easier to turn the head into the most favourable hearing position when using the conventional head-borne hearing aid than when using an apparatus with two microphones.

It should however be possible to get an impression of the effect of the hearing aid on the DTI under certain conditions by using the standard diagram. In using the diagram as demonstrated in this paper the deviations in the results of the measurements affects the reliability of the points plotted. Provided this is taken into account together with the fact that our experimental listening conditions diverge from conditions met with daily (Tonning, 1971 *b* 1972 *a* and *b*) the standard diagram would be of help in making an evaluation of the effect of the hearing aid treatment.

ZUSAMMENFASSUNG

Die gerichtete Verständlichkeitsschwelle (DTI Directional Threshold of Intelligibility) wurde bei 20 Patienten mit praktischer Taubheit auf einem Ohr und herabgesetzter Hörfähigkeit auf dem anderen Ohr untersucht. Die DTI wurde sowohl mit als auch ohne Hintergrundgeräusch, mit und ohne Hörgerät gemessen. Sämtliche Patienten wurden mit einer speziellen Form von Hörgeräten untersucht. Mikrophone wurden an beiden Ohren angebracht, und Impulse von diesen wurden an das bessere Ohr übergeleitet. Sieben Patienten wurden ausserdem mit einem hinter dem besseren Ohr angebrachten Hörgerät untersucht. Die erst genannte Behandlung schien bessere Resultate zu geben.

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CYTOPLASMIC PROCESSES IN NORMAL AND IN MALIGNANT ORAL EPITHELIUM

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Abstract The cytoplasmic processes in preinvasive and invasive carcinoma of the human oral epithelium were examined and compared with the corresponding structures of the normal epithelium. Two types of cytoplasmic processes occur in the intercellular space of both normal and pathologic epithelium. One type is long and slender the other wide-based, tonofilament-containing and associated with desmosomes. The distribution of the cytoplasmic processes varies between the different cellular strata of the normal epithelium.

In preinvasive and invasive carcinoma, where there is great variation in stratification regularity both types of cytoplasmic processes vary widely in number from cell to cell, and additional types of cytoplasmic processes appear in the intercellular space.

The border between the basal cell and the connective tissue is characterized, in the normal tissue by a certain regularity and the presence of a continuous basement membrane. In carcinoma this border is irregular and the basement membrane may be absent, extremely thin, multilayered or composed of an atypical material. The presence of various cytoplasmic processes, all without a basement membrane contributes to the irregular pattern. There are also changes in the subepithelial tissue the normal pattern, dominated by collagen fibrils, is destroyed and replaced by electron-lucent areas. It was suggested that the destructive activity is an early feature preceding the invasive process. It was concluded that these prevailing and well-defined changes may be of diagnostic importance and provide information on the migratory activity of the malignant cell.

In the human oral epithelium, cytoplasmic processes appear in the intercellular space and extend from the basal surface of basal cells. Cytoplasmic processes, extending from cancer cells into the connective tissue, in the absence of a basement membrane have been discussed in relation to the problem of malignancy. They have been regarded as an early sign of invasiveness (Ashworth et al. 1961). In a previous article (Frithiof 1969) it was shown that absence of the electron microscopic basement membrane is a most frequent morphologic deviation from normality in preinvasive and invasive carcinoma. The condition of half-desmosomes, and fibrillar and filamentous components in the basement membrane region in association with various types of changes in the basement membrane, has also been described in a separate paper (Frithiof 1971).

In the present study attention is focused on the cytoplasmic processes as seen in the intercellular space and in the basement membrane region. Their structure and distribution are normally part of a pattern characteristic of the type of epithelium and the position of the cell in a certain stratum of the tissue. In carcinoma *in situ* and in invasive carcinoma, relevant areas are characterized by great variation in stratification regularity and by the presence of additional types of cytoplasmic processes. The purpose of this paper is therefore to describe and discuss these differences as seen in the human oral epithelium and to interpret the observations in terms

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Table I. *Material Age and sex distribution*

Diagnosis	No of specimens	Age groups (years)				Sex	
		11 30	31–50	51–70	71–	Male	Female
Normal non-keratinized	9	2	7			7	2
Normal keratinized	12	5	6	1		6	6
Carcinoma *in situ*	13		3	8	2	10	3
Invasive carcinoma	10	1	2	3	4	7	3
Total	44	8	18	12	6	30	14

of function, in an attempt to evaluate the relation of the differences to the malignant process.

Certain terms used in the following have been defined in a previous article (Frithiof 1971).

MATERAL AND METHODS

The material consists of 44 specimens;[1] 21 from keratinized and nonkeratinized, normal, human, oral epithelium and 23 from pathologic epithelium. The material of pathologic epithelium includes 13 specimens of carcinoma *in situ* and 10 specimens of invasive squamous cell carcinoma of the oral cavity (Table 1). The diagnoses[2] were made under the light microscope on paraffin-embedded material. Excised specimens were cut in two pieces which were immediately fixed, one in a neutral buffered 7% formaldehyde solution for light microscopy and the other in a cold, buffered 1% osmium tetroxide solution for electron microscopy Specimens for electron microscopy were dehydrated in ethanol or acetone, and embedded in Epon and Vestopal respectively Thin sections, stained in solutions of uranyl acetate and lead acetate were studied in a Siemens Elmiskop I. Measurements were made on glossy prints with a magnifying glass (×8) focused on a scale graded in 0.1 mm. A detailed account of the methods has been given in a previous publication (Frithiof 1971)

[1] The material has been collected at the Department of Otolaryngology Karolinska Sjukhuset, and the Department of Oral Surgery Faculty of Dentistry Karolinska Institutet, Stockholm.

[2] Normal specimens have been checked by Associate Professor Bengt Lagerlöf at the Institution of Pathology Karolinska Sjukhuset. The pathological material was classified in cooperation with Associate Professor Gunnar Moberger at the Institution of Tumour Pathology Karolinska Sjukhuset. A detailed account of the material and the diagnostic criteria was given in a previous publication (Frithiof, 1969).

OBSERVATIONS

Normal Material

Cytoplasmic processes in the intercellular space

In the oral epithelium neighbouring cells are partly separated by an intercellular space which is traversed by cytoplasmic processes from the epithelial cells. Generally the intercellular space is wider between basal and spinous cells than between the flattened superficial cells. Certain differences exist in the concentration and distribution of cytoplasmic processes in the non-keratinized and keratinized epithelium.

Non-keratinized epithelium. Two types of structurally different cytoplasmic process project from the cellular surface of basal and spinous cells (Figs. 1 2). One type, which is wide-based and contains tonofilaments, approaches either a corresponding process or the flat surface of the opposed cell and forms a desmosome. Quintuple-layered membrane junctions occur usually close to the desmosomes. The second type of cytoplasmic process is usually not associated with intercellular

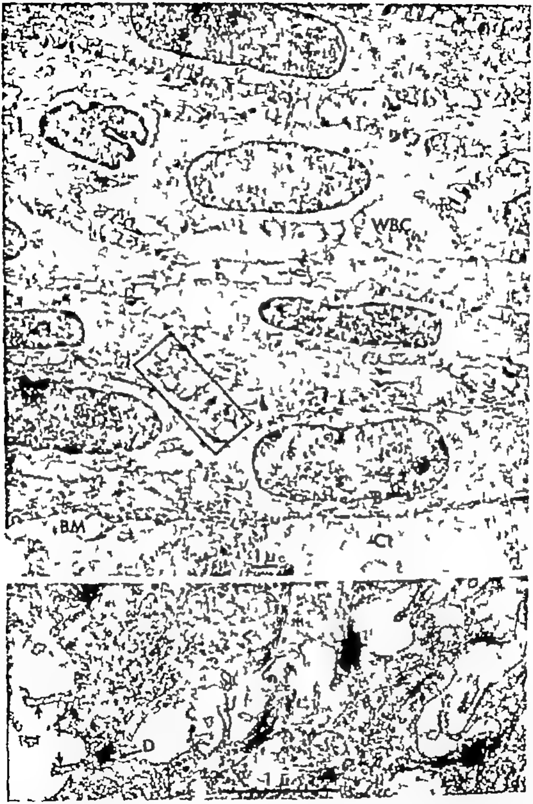
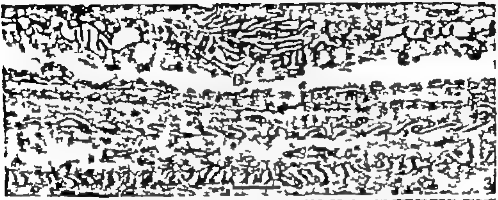


Fig. 1. Normal vestibulum. A continuous basement membrane (*BM*) is situated between the epithelium and the connective tissue (*Ct*). The basal surface of the basal cells (*B*) is mainly flat and devoid of cytoplasmic processes. White blood cells (*WBC*) are normally seen in the intercellular space. × 6 000. (*a*) (*Inset*) Desmosomes (*D*) are associated with wide-based processes, containing filaments. There are also slender processes approximately uniform in thickness. × 30 000.



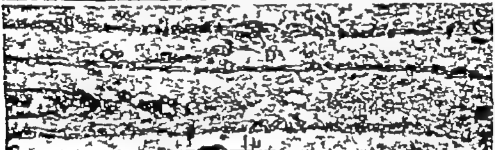


Fig. 2. Normal vestibulum. Stratum spinosum in an area close to the flattened cell layer. The general morphology is maintained throughout the stratum spinosum. Vestopal, 35 000.

Figs. 3–4. Normal vestibulum from two different specimens. Flattened cell layer. The intercellular space is narrow (*arrows*). Slender cytoplasmic processes form an interdigitating pattern. The number of desmosomes (*D*) is reduced. Epon, 12 000.

Fig. 5. Normal vestibulum, the flattened cell layer (same specimen as in Figs. 2 and 1). The narrow intercellular space (*arrows*) is more or less com-
are reduced in number. Vestopal, 30 000.
pletely filled with dense material. The desm-

Fig. 6. Normal gingiva. Stratum basale. There is a large number of cytoplasmic processes in the intercellular space compared with Fig. 1. Cytoplasmic processes extending into the connective tissue are covered by a continuous basement membrane (*BM*). Dense masses of collagen fibrils constitute the subepithelial connective tissue (*Ct*). Epon. ×6000. (*a*) ×[illegible] 900. (*b*) × 42 000

contacts. It is thinner and devoid of tonofilaments. Each process is approximately uniform in thickness (~500 A) and contains a central dense core. The latter is visible as a thin line in longitudinally sectioned processes and as a central dot in those transversely sectioned. Adjacent processes may differ in length and curvature, but are very similar in thickness and structure. Within the flattened cell layer the slender cytoplasmic processes tend to increase in number and decrease in length (Figs. 3–5). Slender processes, with al-

Fig. 7 Normal gingiva from the same specimen as in Fig. 6 Stratum spinosum, 2–3 cells from the basement membrane. The wide-based cytoplasmic processes are numerous with well developed desmosomes and with dense bundles of tonofilaments. Epon, ×7 200.

Fig. 8 Normal gingiva, lower part of Stratum spinosum. There are dense bundles of tonofilaments (*tf*) in the wide-based processes. *D* = Desmosome. Epon, 60 000.

most constant dimensions and almost regular distribution, frequently correspond to shallow invaginations in the apposed cell, and form an interdigitating pattern. In superficial cell layers desmosomes are rare. They appear in areas where the comparatively smooth surfaces of apposed cells approach one another in the absence of the slender processes.

Keratinized epithelium. In basal and spinous layers of keratinized epithelium, both types of cytoplasmic process are far more numerous than in non-keratinized epithelium (Fig. 6). The slender intermingling processes, with an irregular course, practically fill the intercellular space between the basal cells. In the stratum spinosum there is a gradual increase in the number of tonofilament-containing, wide-based processes, associated with desmosomes and quintuple-layered junctions, and a decreasing number of slender processes (Figs. 7, 8). In the presence of white blood cells in the intercellular space there are no remnants of detached desmosomes. Throughout

Fig. 9. Normal gingiva, Stratum granulosum and corneum. The intercellular space (*I*) is narrow and the cytoplasmic processes are absent. N = Nuclear remnant. Epon. × 15 000.

Fig. 10. Normal gingiva, Stratum granulosum and corneum. Desmosomes (*D*) appear where the flat or slightly elevated surfaces of apposed cells are closely related. Epon. × 60 000.

the stratum spinosum and the stratum granulosum rows of desmosomes, with short, dense bundles of tonofibrils, appear as the most conspicuous pattern of the tissue at low magnification marking the main outline of the individual cell. In the flattened cells of the stratum granulosum, the wide-based cytoplasmic processes are shorter than in the underlying layers (Figs. 9, 10). The slender processes decrease in number and the plasma membrane is less convoluted. In the stratum corneum cytoplasmic processes are rare (Figs. 9, 10). The intercellular space is narrow and the desmosomes seem to decrease in number. They appear where the flat or slightly elevated surfaces of apposed cells are closely related.

Cytoplasmic processes in the basement membrane region

The wide intercellular space between the basal cells is reduced at its most basal point to a ~300-Å-wide gap, forming the communication between the intercellular space and the lamina lucida. In the sectioned tissue the gap appears to be formed by slender processes approaching each other from opposed basal cells. This narrow gap has not been observed to be substantially widened or occluded with dense intercellular material or by membrane fusion. When the basal cells are separated by a white blood cell, situated partly in the intercellular space and partly in the connective tissue, a narrow space, forming a communication between the intercellular space and the lamina lucida, is also maintained, as the slender ridges from the basal cells approach the blood cell. The edge of the basement membrane is also closely related to the white blood cell.

Cytoplasmic processes, extending from the basal surface of the normal basal cell, are different from processes in the intercellular space. There are also characteristic differences between the non-keratinized and keratinized epithelium.

Non-keratinized epithelium. The basal surface of the basal cells is mainly flat and devoid of cytoplasmic processes (Fig. 1). The basement membrane is continuous and associated with aperiodic fibrils. In the adjacent connective tissue there is a high concentration of collagen fibrils, arranged in bundles.

Keratinized epithelium. In contrast to the non-keratinized epithelium, the basal surface of the basal cells is composed of two or more cellular processes per section, whose length and diameter exceed 2 μ and 0.5 μ respectively (Fig. 6). These processes are completely covered by a continuous basement membrane, and a large number of half-desmosomes. There are no slender processes of the type observed in the intercellular space. The subepithelial connective tissue is characterized by a high content of collagen fibrils.

Pathologic Material
Preinvasive and Invasive Carcinoma

Cytoplasmic processes in the intercellular space

Cells in relevant areas display cytoplasmic processes of the desmosome-carrying and slender types. Some cells contain only a few desmosomes per section, but, occasionally desmosomes are very abundant (Figs. 11, 12). Quintuple-layered junctions are found close to some of the desmosomes. Obvious variations in length and concentration of the slender processes are also observed (Fig. 12). The width of the intercellular space may be substantially increased without having any relation to the concentration of the slender processes (Fig. 13).

In addition to the normal cytoplasmic processes a more voluminous, bulging process, connected with the rest of the cell by a narrow string of cytoplasm, is frequently observed (Figs. 13, 14). Its content may differ morphologically from the main part of the cytoplasm. Tonofilaments are markedly few, but the ribosome-like particles vary between a very low and an extremely high concentration (Figs. 13, 14). Bulging processes, some almost free from organellae, and others completely filled with dense particles, may be seen to extend from the same cell. Processes, filled with dense particles, are also found in multilobular aggregates originating from a common cytoplasmic stem. Free ribosome-like particles and fragmented, membranous material (Figs. 13, 14) are frequently observed in the intercellular space.

Cytoplasmic processes in the basement membrane region

Cytoplasmic processes, extending from the basal surface of cells facing the connective tissue, are common. Three main types can be distinguished.

The bulging type (Figs. 15, 16), without to-

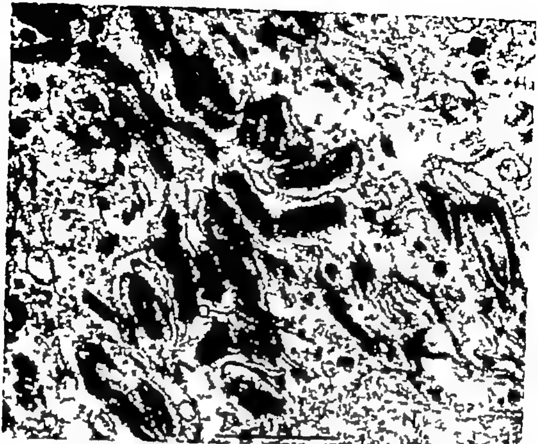


Fig. 11. Squamous cell carcinoma. There are areas with a high concentration of well developed desmosomes. N = Part of a nucleus. Q = quintuple-layered junction. Vestopal. 30 000

Fig. 12. The same specimen as in Fig. 11. In so regions, the desmosomes are rare and poorly dev oped (*D* = desmosome-like contacts). In the select area there is a high concentration of slender processe Vestopal. 30 000.

nofilaments and with or without ribosome like particles, was found in 14 specimens. The size of the processes ranged from single lobules, about 0.2 microns in diameter projecting through, and not covered by the basemen membrane, to huge multilobular masses sev eral microns in diameter and extending int the loose connective tissue. Extracellular ribo-

Fig. 13. Carcinoma *in situ* close to the basal cells. Bulging processes (*arrows*) connected with the rest of the cell by a narrow string of cytoplasm, are frequently recognized. Here, they contain only a few ribosomes. The intercellular space is wide. Cytoplasmic structures are seen in the intercellular space (*arrowheads*). Epon, × 9 000.

Fig. 14. Squamous cell carcinoma, central part of the epithelium. There are cytoplasmic processes, bulging with ribosome-like particles (*arrow*). Cytoplasmic structures are seen in the intercellular space. Epon, × 8 800. (*a*) (*inset*) There is a high concentration of ribosome-like particles in the cytoplasmic process compared with the rest of the cytoplasm. × 29 300.

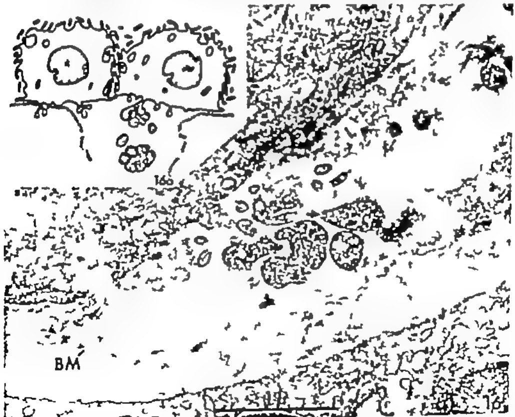


Fig 15 Squamous cell carcinoma facing the connective tissue. Cytoplasmic processes of the bulging type (*arrows*), extend through an incomplete basement membrane (*BM*). They are surrounded by electron-optically empty spaces. Epon, 18 000.

Fig 16 Squamous cell carcinoma. Cytoplasmic processes (*arrows*) bulging with ribosome-like particles are surrounded by wide, structurally empty spac The basement membrane (*BM*) is separated from t cancer cell and fragmented. Vestopal, ×30 000 (Outline of cancer cells with bulging processes (*arro heads*) extending through the basement membra The basement membrane is separated from the cel

Fig 17 Squamous cell carcinoma facing the connective tissue. Long, straight and narrow cytoplasmic processes (*arrows*) extend into the loose connective tissue (*Ct*). The basement membrane is mainly absent in the selected area. The collagen fibrils are replaced by granular and filamentous structures. Vestopal, ×24 000. (*a*) Outline of cancer cells with long, slender cytoplasmic processes in absence of a continuous basement membrane.

some-like particles and fragmented membranous material may be present in such areas.

The second type, which was found in 11 specimens in absence of the basement membrane, includes straight and narrow processes containing filaments, but mainly devoid of ribosomes (Fig. 17). Some processes are situated deep in the loose connective tissue and are recognized by their constant diameter which approximates that of the slender processes in the intercellular space.

The third type was observed in only two specimens, in cells almost free from ribosomes and in absence of a normal basement membrane. The thin processes are characterized by their close association with islands of basement-membrane material which they surround either completely or as crescents (Fig. 18).

According to these observations, the basement membrane is absent or incomplete in preinvasive and invasive carcinoma in association with the different types of cytoplasmic processes extending from the basal cell (Figs. 15–18). In addition, there are wide electron-optically empty spaces, usually surrounding the cytoplasmic processes, and in other areas where the basement membrane is missing (Figs. 15–18). The collagen fibrils are also remarkably scarce in such areas, and are replaced by granular and filamentous structures (Figs. 15–18)

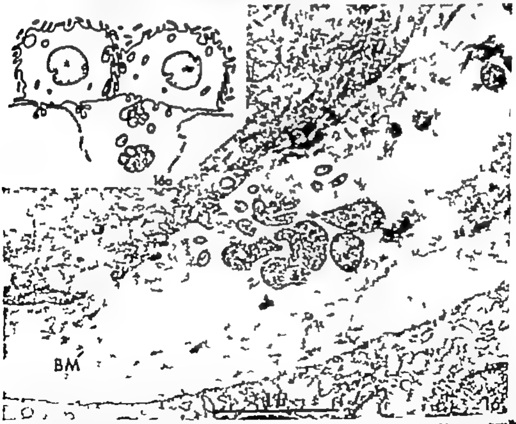


Fig. 15. Squamous cell carcinoma facing the connective tissue. Cytoplasmic processes of the bulging type (*arrows*), extend through an incomplete basement membrane (*BM*). They are surrounded by electron-optically empty spaces. Epon, × 18 000.

Fig. 16. Squamous cell carcinoma. Cytoplasmic processes (*arrows*) bulging with ribosome-like particles are surrounded by wide structurally empty ... The basement membrane (*BM*) is separated from ... cancer cell and fragmented. Vestopal, × 30 000. (... Outline of cancer cells with bulging processes (arrow*heads*) extending through the basement membra... The basement membrane is separated from the

cess of time presumably is spent on the realization of the effect of TT contraction on the middle ear impedance-matching mechanism.

The enhancement of CM amplitude following TT contractions in cases when auditory stimuli of high intensities are employed, may be explained in terms of known correlations between CM amplitude and sound intensity. The linear part of the CM input–output curve (CM amplitude as a function of the sound intensity) is generally known to transfer to its non-linear part at high acoustic pressures, i.e. an increase in sound intensity does no longer result in proportional enhancements of CM amplitude or at higher intensities, it remains unchanged or even diminishes. In the latter case a decrease of the intensity of sounds transmitted to the cochlea will be certainly followed by an enhancement of CM amplitude.

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ZUSAMMENFASSUNG

Der Einfluss einer direkten elektrischen Reizung des M. tensor tympani auf die Schalleitung ist frequenzabhängig: eine ausgeprägte Verminderung (bis auf 5–10 dB) von Mikrophonpotenzialen kann im Bereich von 0.5–0.8, 1 kHz beobachtet werden, die Leitung von Hochfrequenztönen (z. B. hoher als 4–6 kHz) scheint nur wenig verändert zu sein während im Bereich von 1.8–2 kHz sogar eine Steigerung der Amplitude von Mikrophonpotenzialen stattfindet. Die Abhängigkeit dieser Wirkung von den Parametern des Reizstromes und der Charakteristik der Muskelkontraktion (Latenz, Kontraktionsdauer, Ermüdung) wurde untersucht. Experimentelle Befunde, die den Einfluss der Kontraktion des M. tensor tympani auf die evozierten Potenziale des achten Nerven und der Cochlearkerne betreffen, werden vorgeführt. Die Ergebnisse weisen auf eine Teilnahme des M. tensor tympani im Akkomodationsmechanismus des Mittelohres hin.

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ON THE USE OF ACOUSTIC MIDDLE EAR MUSCLE REFLEXES IN STUDIES OF AUDITORY FUNCTION IN NON-ANESTHETIZED RABBITS

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Abstract Use of the acoustic middle ear reflexes for studies of the function of the auditory pathways in non-anesthetized animals was investigated. Middle ear muscle activity was recorded in rabbits as changes of the acoustic impedance at the eardrum. The stimulus–response curves were found to be well described by the Gaussian distribution function with mean value *A* and variance B^2 The reproducibility of the stimulus–response curves of the ipsilateral middle ear reflex obtained from repeated measurements was statistically analysed. The standard deviation was 1.9 dB for the position along the intensity axis (*A*) and 1.0 dB for the slope of the curve (*B*). The variability of the reflex recording in repeated measurements during single experimental sessions was on the order of 1.0 dB (*A*). The optimal measuring tone intensity range was between 66 and dB SPL.

Peripheral and central auditory mechanisms have been studied by using a diversity of motor reactions (see e.g. Forbes & Sherrington, 1914 Cemach 1920 Spiegel & Kakeshita, 1926 Anderson & Wedenberg 1965). In animal experiments, contraction of the middle ear muscles (Kato 1913 Lorente de Nó & Harris, 1933 Kobrak et al. 1935 Kobrak, 1957 Simmons, 1964 *b* Borg, 1971) and movements of the pinna (see e.g. Gerstner 1942) have been the most commonly used reflexes for this purpose. The value of these methods in auditory studies is often reduced by the use of anesthetized animals or by the difficulty encountered in determining only reflex threshold.

Using a method developed by Møller (1960, 1961) middle ear reflex activity can be simultaneously recorded bilaterally as changes in the acoustic impedance of the ear The relative response amplitudes over a wide intensity range are easily obtained. It has recently been shown that this method, developed for measurements in man can also be used for middle ear reflex recordings in nonanesthetized rabbits (Borg & Møller 1968) and that the impedance change is a proportional measure of the middle ear muscle activity over a wide intensity range (Borg, 1972 *a*).

As no surgery is required, this latter method is suited for repeated measurements and functional studies in chronic experiments. A prerequisite for using the reflexes in studies of auditory functions is a comprehensive knowledge of the stability of the responses during experimental sessions and the variability between periodic repeated measurements. The reproducibility of the middle ear reflex, measured as impedance changes, was found to be good in man (Møller 1962). In the rabbit, preliminary experiments have shown the long-term variability to be on the order of a few dB (Borg & Møller 1968) However a closer analysis is needed.

This study was supported by Reservationsanslaget, Karolinska Institutet, and by Sällskapet för Medicinsk Forskning.

The aim of the present study was to provide a firmer experimental basis for the use of the middle ear reflexes, measured as changes of impedance, in studies of auditory function. A statistical analysis of the stability and the reproducibility is presented as well as a determination of the influence of measuring tone intensity.

MATERIAL AND METHODS

The experiments were performed on adult rabbits of the small chinchilla strain. Determination of reproducibility was made on 24 rabbits, the short-term stability on 29 rabbits and the influence of the measuring tone intensity on 15 rabbits.

Recording of the middle ear reflex activity

The relative acoustic impedance change at 800 Hz was recorded simultaneously in both ears in response to acoustic stimulation of either ear. The method has been presented in greater detail by Borg & Møller (1968). The measuring devices were hermetically sealed to the ear canals by a dental moulding substance. The measuring tone (800 Hz) and the tone eliciting the reflex activity were electrically balanced out. The stimuli were presented alternately to the left and right ear. Tone bursts of 0.5 sec duration (the rise time to 90% of maximum amplitude and the decay time to 10% were both 2 msec) with a frequency of 2.0 kHz, were used to elicit the reflex. The stimuli were presented with varying intervals, and the intensity was increased in steps of 4 dB from below threshold to the maximum intensity used and then stepwise lowered to below threshold. Thus, two determinations were made at each level of sound intensity used.

Contraction of the middle ear muscles changes the acoustic impedance of the middle ear and upsets the balance of the 800 Hz measuring tone. The resulting output signals from both ears were recorded simultaneously on a two-track tape recorder and later processed. In the investigation of the stability and the reproducibility the measuring tone intensity was 60 or 66 dB SPL.

The amplitude of the impedance change at the end of the stimulus tone was measured and expressed in percentage of the maximum obtainable change. The mean of the two values at each stimulus level was plotted as a function of the stimulus soundpressure level (in dB re 0.0002 μbar). Four stimulus-response (SR) curves, two for ipsilateral and two for contralateral stimulation, were used to describe the series of recorded reflex responses.

During the experimental session, the rabbit was sitting calm and fully awake, in a box open at the top. Anxious or irritated animals could not be used for reflex measurements, since their movements and rapid breathing produced too much noise.

Statistical analysis

The analysis of the variability of the SR curves was performed in three steps. In the first step the SR curves were described by a mathematical function.

$$f(u) = \frac{1}{\sqrt{2\pi}\,B}\int_{-\infty}^{u} e^{-\frac{(x-A)^2}{2B^2}}\,dx \qquad x \text{ is sound}$$

intensity (in dB SPL). The two estimated parameters A and B were used in the analysis to represent the series of primary data. This function is Gaussian distribution function with mean value A and variance B^2 which allows simple computations in fitting it to experimental data.

An artificial frequency histogram was formed from the experimental data by calculating the difference between each ordinate value and the value at a 4 dB lower sound level. The constant value representing the pedestal resulting from the background noise in the recording of impedance change was first subtracted. Thus, the S-shaped SR curves were transformed into bell-shaped histograms.

A histogram formed in this way may have a gross physiologic interpretation. Assuming

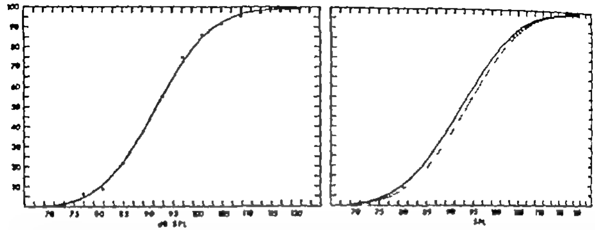

Fig. 1. Left graph. Gaussian distribution function adapted to experimental points (dots). Ipsilateral stimulation with 2.0 kHz. Non-anesthetized rabbit. Ordinate shows relative response amplitude. *Right graph.* Stability of stimulus–response curves. — synthesized from parameters obtained at the beginning of experiments. - - - synthesized from parameters obtained as the average change in the parameters after 1 to 2 hours, at the end of the experiments. Ipsilateral stimulation with 2.0 kHz.

that an increase in response amplitude is determined mainly by the recruitment of equally strong motor units (Bigland & Lippold, 1954; Henneman et al. 1965), every bar of the histogram would show the relative number of motoneurones with thresholds of activation by sound of intensities in the corresponding 4 dB interval. The parameters *A* and *B* represent the mean and the standard deviation respectively, calculated from the frequency histogram by the "differentiated" SR curve.

The aim of the second step of the statistical analysis was to determine the degree to which the curves synthetized from the estimated values *A* and *B* fit the measured SR functions. The Chi-square test was used on each curve

$$\chi^2 = \sum_{i}^{n} \left(\frac{x_i - f_i}{f_i}\right)^2$$

x_i is the experimental point, f_i = the calculated value. 28% of the 314 artifical histograms formed by differentiation of the experimental values of the individual experiments were found to differ significantly ($p < 0.01$) from the calculated Gaussian frequency functions. Inspection of the curves which deviated revealed unsystematic variations in the experimental values. This "noise" component was minimized by using the SR curves based on the average of all the responses at each sound level for each individual ear instead of single experimental curves. Only two of the average curves showed a poor fit ($p < 0.01$), but in these cases results from only two experiments were available.

It can thus be concluded that the experimental SR curves can be properly described by the Gaussian distribution function synthesized with mean value *A* and variance B^2.

In the third step of the analysis the two parameters (*A* and *B*) were used to represent the individual SR curves in determinations of the stability, the reproducibility and the influence of the measuring tone intensity.

RESULTS

Stability of reflex activity in non-anesthetized animals

Sudden movements of the rabbit can change the position of the measuring devices in the rabbit's ear. The resulting change in static impedance is easily seen in the recordings as a discrete imbalance. In 68 experiments on 29 rabbits, a series of measurements were performed over a period of 1 hour or more

without such disturbances. In all these experiments the stimulus–response relationship at 2.0 kHz was determined both at the beginning and at the end of the experiment. The curves obtained at the beginning and at the end of the experiment were compared to determine if systematic changes in reflex properties had appeared during the experimental session.

It was found that the average maximal amplitude was slightly but significantly smaller in the determination at the end as compared to that at the beginning of the experiment (97% of the initial amplitude, $p<0.01$). In order to quantitatively determine changes in the excitability of the reflexes, the Gaussian distribution function was approximated to each experimental curve after normalizing the amplitude to 100%.

Fig. 1 (left graph) shows an example of the experimental points and the approximated curve. Two parameters determine the shape of the curve. The position along the intensity axis is given by parameter A (in this case 92.0 dB) and the slope given by parameter B (in this case 8.9 dB). The error of the fit described by the calculated Chi-square value is 11.9 (eight degrees of freedom). The distribution formed by the differentiated experimental values does not significantly differ from the Gaussian frequency function ($p>0.05$).

The differences between the values of each pair of parameters which described the curves at the beginning and at the end of each experiment were calculated. The right graph in Fig. 1 shows an ipsilateral SR curve obtained at the beginning of an experimental session represented by the function synthetized from the parameters A and B (solid line). The broken line shows the function representing the average change in the parameters. On the average the parameter A was increased, 1.2 dB (standard deviation S.D = 3.2 dB), i.e. the curve was shifted to higher intensities. The parameter B the "slope" was increased 0.1 dB (S.D = 1.8 dB). Whereas the shift was slight but significant ($p<0.01$), the change in the slope was not significant ($p>0.1$).

Influence of the intensity of the measuring tone on the stimulus–response pattern

Although the intensity of the measuring tone (800 Hz) was always kept at an intensity well below the reflex threshold, interaction with the stimulus tone could not be excluded. In order to settle a possible influence, the intensity of the measuring tone was varied in 6 dB steps, between 60 and 78 dB SPL, during the same experimental session.

Assuming that reflex excitability is independent on measuring tone intensity a 6 dB increase in the intensity of the 800 Hz tone should result in a doubling of the response amplitudes for physical reasons. The maximal amplitudes obtained at the various measuring tone intensities deviated only a few percent from the expected values. The average differences were not significant ($p>0.05$). It was assumed that these differences to a large part were due to variability in setting the intensity of the measuring tone.

The stimulus–response functions were described by the Gaussian distribution function after normalizing the amplitude to 100%. In each experiment the ipsilateral curves obtained at the four measuring tone intensities were described by the function. The parameters (A and B) for the curve at 66 dB SPL measuring tone intensity was used as the reference. The average difference between the reference and each of the other intensities was calculated for both A and B.

Fig. 2 shows the synthesized SR curves representing the average relation of the curves obtained at the four measuring tone intensities. It is seen in Fig. 2 that some variability appears in the curves. There is, however, no significant ($p<0.05$ t test) systematic difference between the measuring tone intensities of 60, 66 and 72 dB SPL. The parameter A at the highest measuring tone intensity (78 dB SPL) was slightly (2.4 dB) but significantly

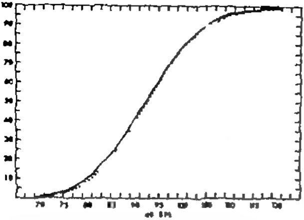

Fig 2 Influence of intensity variation of 800 Hz measuring tone on the functions synthesized from the parameters *A* and *B* The 66 dB curve (—) was used as a reference, 60 dB ( ), 72 dB ( ), [illegible] dB ( ). Ipsilateral stimulation with 2.0 kHz. Non-anesthetized rabbit.

($0.001 \leq p \leq 0.05$ *t*-test) increased compared with the reference intensity (66 dB SPL)

The amplitude of the background noise level is independent of the measuring tone intensity since it originates mainly from noise caused by breathing of the rabbit. The signal-to-noise ratio will thus increase when the impedance change signal is increased which happens when the intensity of the 800 Hz measuring tone is increased.

eproducibility

Measurements of the ipsilateral reflex responses were repeated up to 11 times in 38 ears of 24 rabbits with intervals ranging from one day to more than a year The experimental SR curves for each ear were described by the mathematical function used. The derived parameters (*A* and *B*) characterized the curves and formed two series of values for each ear The individual variations in the variability of the parameters were investigated. It was found that the variance of the slope (parameter *B*) did not differ significantly between the different ears (Bartlett's test, $0.1 > p > 0.05$) There was a barely significant difference ($0.02 < p < 0.05$) for the variance of the shift along the intensity axis (parameter *A*).

On the basis of these results, it appeared reasonable to use the common estimate of the variance of *A* and *B* for all rabbits. It was further found that the distribution of the parameters *A* and *B* did not differ significantly from a normal distribution (Chi-square test, $p > 0.2$). Since the coefficient of correlation between *A* and *B* was low the parameters could be regarded as independent in the further statistical analysis. The highest correlation coefficient obtained was 0.46, which is not significant at the 5% level. The common estimate of the standard deviation was 1.9 dB for parameter *A* and 1.0 dB for parameter *B*.

These values can be used to estimate the minimum separation between two SR-curves which must exist if the curves should be regarded as significantly different. Such information becomes of interest when the middle ear reflexes are used to study functional alterations in the lower auditory system, e.g. as a result of surgical lesions.

Fig. 3 shows an example of a series of curves drawn with parameters representing the smallest significant differences in position along the intensity axis (left graphs) and in the slope (right graphs). The upper graphs represent the limits for significance at the 0.05 level the lower graphs represent limits at the 0.01 level. The heavy solid line in each graph shows the normal reflex properties before alterations calculated from one, two, or four experimental curves. The parameters representing the normal reflex properties are arbitrarily chosen. The limits for cases with one two, or four experiments made before and after the operation are shown by the thin solid lines, the broken lines, and the dotted lines, respectively An experimentally obtained SR curve after a lesion falling in part outside the corresponding limits thus implies a significant alteration in the auditory system.

The reproducibility of the crossed reflex was not analysed statistically No systematic difference with regard to reproducibility has been observed between ipsilateral and contralateral reflexes when series of curves were plotted on the same graphs and visually compared.

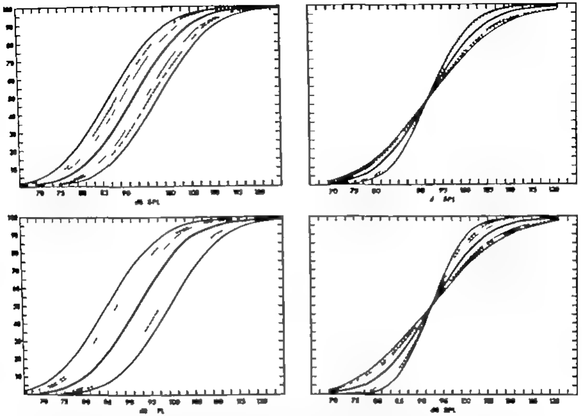

Fig 3 Reproducibility of stimulus-response curves. Limits for significance at 0.05 level (upper graphs) and at 0.01 level (lower graph) for deviation between a reference curve (thick continuous line) and curves obtained on another experimental occasion. Left graphs show shift along intensity axis (parameter *A*); right graphs show change in slope (parameter *B*). The thin lines show the limits calculated assuming one (—), two (-) or four ( ) experiments as basis for both curves to be compared.

DISCUSSION

Utilization of the middle ear reflexes as measuring instruments in auditory experiments

Both acute and chronic experiments involve a comparison of the reflex properties before and after alterations in the auditory system. Knowledge about the stability and the reproducibility of the measurements is a prerequisite for the use of the reflex for this purpose. In man the reproducibility of the SR curves of impedance changes is within 1–2 dB (Møller 1962 see also Feldman & Zwislocki, 1965). In most earlier animal experiments, the variability appears considerable both during single experiments and for repeated measurements (cf however Kobrak et al. 1935 Simmons, 1965). The results of the present study are in contrast in that respect with studies using chronically implanted electrodes in the middle-ear muscles and on the round window in the cat (Simmons, 1963 1964 *a*, *b* Simmons & Beatty 1964 Baust & Berlucchi, 1964). The present study shows good stability and reproducibility

Recordings of the impedance changes require standardized experimental conditions to minimize noise produced by the animal (Borg & Møller 1968) Such restrictions have not regularly been included in studies with implanted electrodes. In the latter case, the influence of habituation, orienting and startle reactions have probably contributed the variability of the recordings (Simmons & Beatty 1964 Simmons, 1964 *a*). However rabbits, especially the calm chinchilla strain used in

the present study might be superior to cats in allowing stable recording conditions. It can also be noted that electrical stimulation of sympathetic centres in the diencephalon increases the speed of habituation of orienting reactions in non-anesthetized animals (Koyama et al. 1966). The rapid habituation observed in experiments on cats might thus be due to a high activity in brain sympathetic centres.

The impedance change as used in the present study *is a relative measure of the reflex* response. A scalar change of the response amplitudes could thus possibly occur without influencing the SR function. However, saturation of the response amplitude is a property *of the reflex arc at or after the level of the* motoneurones. This is shown, for example, by the fact that the amplitude of the m. tensor tympani response increases above the intensity giving maximal m. stapedius response (Werdäll 1958) or a *maximal response of the total reflex* (m. stapedius and m. tensor tympani in conjunction, Borg 1972*b*). Even proportional changes in the excitability of the ascending auditory pathway will thus be revealed as changes in the shape of the SR function. When unilateral alterations are made in the auditory pathway it is furthermore possible to compare responses in one ear elicited from [illegible]ther side, one of the reflex arcs remaining [illegible]tely unchanged. In such cases even very small proportional changes can be detected.

Choice of measuring tone

Factors important for the choice of frequency of the measuring tone used for recording the impedance change have been analysed by Møller (1961). *He found that 800 Hz was most* favourable in human experiments. The main disadvantage in using lower frequencies is increased sensitivity to small changes in the position of the measuring devices. Higher *frequencies* than 800 Hz give smaller impedance changes and thus a poor signal-to-noise ratio. In the rabbit, a higher measuring frequency could be used because the resonant frequency of the middle ear (Møller 1965) is higher than it is in man, but since the animal usually produces some noise (breathing and movements) the frequency 800 Hz was also choosen in the animal experiments.

The intensity of the measuring tone is kept well below the reflex threshold at this frequency (80 to 90 dB SPL, Borg & Møller, 1968). Interaction has, however, been found to occur between two simultaneous tones even when one of them is below the threshold. Furthermore Terkildsen et al. (1970) found small changes of the crossed reflex response in man when the measuring tone was changed from 70 to 75 dB SPL. The present study *showed no significant effect of changing the* intensity from 60 to 72 dB SPL. However the highest intensity used, 78 dB SPL, gave a small decrease of the reflex excitability. The lowest intensity used, 60 dB SPL, usually resulted in a poorer signal-to-noise ratio and the most favourable intensities were in the range from 66 to 72 dB SPL.

ZUSAMMENFASSUNG

In der vorliegenden Arbeit wurde die Reaktion des akustischen Mittelohrreflexes als ein Mass der Funktion der Gehörbahnen an nichtbetäubten Tieren auf ihre Reproduzierbarkeit und Variabilität hin untersucht. Zu diesem Zwecke wurde die Aktivität der Mittelohrmuskeln an Kaninchen als Änderung der akustischen Impedanz am Trommelfell aufgenommen. Wie die Auswertung ergab, konnten die Reaktionskurven auf die Stimuli recht gut durch die Gauss'sche Verteilungsfunktion mit dem Mittelwert A und der mittleren statistischen Abweichung (standard deviation) B beschrieben werden. Die aus wiederholten Messungen gewonnenen Reaktionskurven des ipsilateralen Mittelohrreflexes wurden auf ihre Reproduzierbarkeit hin statistisch analysiert. Wie sich daraus ergab, war die mittlere statistische Abweichung in der Veränderung der Kurvenlage längs der Intensitätsachse (A) 1,9 dB und hinsichtlich der Neigung der Reaktionskurve, die durch B ausgedrückt ist, *1,6 dB*. Die Variabilität der Reflexaufzeichnung bei wiederholten Messungen an dem gleichen Tier im Verlauf von ein bis zwei Stunden war in der *Grösse von 1,0 dB*. — Weiterhin wurde die optimale Intensität des Messtones von 800 Hz untersucht. Sie liegt bei einem *Schalldruckpegel* (SPL) von 66–72 dB. Bei niedrigerem Schalldruck wird das Signal-Stör-Verhältnis ungünstiger während bei höherem Schalldruckpegel die Gefahr vorliegt, dass die Reflexreaktion beeinflusst wird.

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THE THRESHOLD OF THE STAPEDIUS REFLEX FOR PURE TONE AND NOISE STIMULI

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Abstract The Zwislocki acoustic bridge was used to study the acoustic stapedius reflex in 30 normal young adults. The stimuli were bursts of white noise, narrow bands of noise centered at 2 000 and 4 000 Hz, and pure tones of 250, 2 000 and 4 000 Hz. An electroacoustic data recording system was substituted for the aural monitoring system that is normally used with the Zwislocki bridge· the sensitivity of the system was such that it allowed identification of one to two decibel changes in the probe tone level. The mean threshold values for the pure tones studied were 81 dB SL, while the means associated with the several noise stimuli were 62 dB SL. The thresholds for the noise stimuli were found to be significantly more stable than those for pure tones.

In 1946 Metz published his classic monograph in which he demonstrated that an impedance bridge could be used to monitor contractions the stapedius muscle The work of Metz [illegible] to numerous clinical and theoretical stud of the acoustic reflex in humans and animals.

Considerable variability can be found in the literature dealing with the threshold of the stapedius reflex in man. Jepsen (1951) used an impedance monitoring technique and found thresholds of about 80 dB sensation level (SL) for the 250 to 4 000 Hz range. In 1952 Metz, using a technique similar to Jepsen's, found thresholds varying from 70 to 90 dB SL for pure-tones. Weiss et al. (1962) used tympanomanometry to determine the threshold level of the human stapedius reflex and found mean values of 96 to 107 dB SPL for the 400 to 6 400 Hz range.

Both Dallos (1964) and Lilly (1964) have used the Zwislocki acoustic bridge to study the stapedius response to a white noise stimulus. Dallos found a mean reflex threshold of 72 dB SL, while Lilly reported a mean of 68 dB SL.

The purpose of this study is to systematically compare the stapedius response to pure-tone and noise stimuli threshold levels and stability of the reflex threshold will be investigated.

PROCEDURES

The Zwislocki acoustic bridge was used to monitor the contractions of the stapedius muscle for this study The standard technique for monitoring the probe tone with the Zwislocki bridge is through the stethoscope that is attached to the bridge. For this study the stethoscope was removed and the bridge was coupled to a one-inch condenser microphone by means of a short length of stethoscope tubing and a specially built brass adapter The signal was fed from the bridge to a B and K audio frequency spectrometer which contains a third octave filter and a vacuum-tube voltmeter. The filter was set to center on 500 Hz, which was the probe tone frequency used throughout this study The spectrometer allowed display of the signal from the bridge on the meter or the signal could alternatively be routed, after filtering, to a graphic level recorder To further reduce the ambient noise

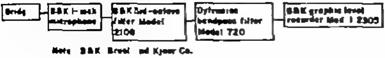

Fig 1 Block diagram of the data recording system.

in the system, a band-pass filter was placed in line between the spectrometer and the recorder (Fig. 1). The recorder was generally used with a writing speed of 8 inches per second and a paper speed of 1 millimeter per second. This combination seemed to offer the clearest data tracing for most subjects.

The use of a visual display apparatus with the acoustic bridge has several distinct advantages over aural monitoring. With this system, the hearing sensitivity of the experimenter is not a confounding variable. Furthermore, permanent records are available for comparison of scorer judgments and further data analyses.

The stimuli used for this study were 500 ms bursts of white noise, narrow bands of noise centered at 2 000 and 4 000 Hz, and pure tones of 250, 2 000 and 4 000 Hz. The stimuli were pre-recorded on tape in a series of 16 two-decibel increments covering a test range of 30 dB, using an Ampex PR 10 two channel tape recorder. The rise and fall time was set at 10 ms, and a 5 000 ms delay was allowed between stimuli. Presentation levels were available from 50 to 110 dB SPL, each of the six noise and pure tone stimuli was presented in at least two consecutive ascending series. Fig. 2 is a block diagram of the system used to deliver the stimuli. The same TDH 39 earphone was used for stimulus presentation and auditory threshold measurements.

The subject was in a prone position on a standard examination table with his left ear downward. The left ear rested on a TDH 39 earphone which was fitted into a foam rubber pillow for comfort. The acoustic bridge was supported by a specially built apparatus which was bolted to the examination table. The only instructions given to the subject were to lie as still as possible and not to talk unless absolutely necessary.

After the bridge was properly fitted into the right ear it was balanced using the decibel meter on the spectrometer; finer adjustments were made by observing the pen of the graphic level recorder. When the point of minimal intensity of the probe tone was found, the first stimulus sequence was presented.

The sensitivity of the system was such that changes of one decibel in the probe tone level were measurable.

The subjects for this study were 30 young normal hearing adults. Responses were obtained from at least 29 of the 30 subjects to all stimuli except the 4 000 Hz pure-tone, to which only 15 subjects responded, and to the 250 Hz pure-tone, which yielded results in only 4 subjects.

RESULTS

Fig. 3 shows sample response recordings for several subjects. The arrow indicates the first accepted muscle response. The inverted tracing for subject 16 is typical of the tracing received with the bridge adjusted to slightly off the null point.

Table I summarizes the means, standard deviations and sample sizes for the six stimuli employed.

The thresholds for the three noise stimuli are within a small range (61.57, 61.62 and

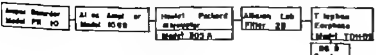

Fig 2 Block diagram of the stimulus delivery system.

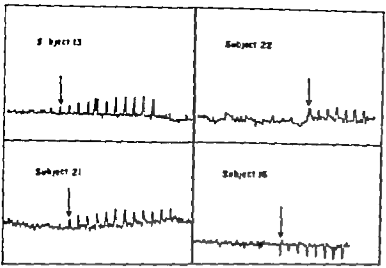

Fig. 3. Sample response recordings.

62.10 dB SL). The responses to the 2 000 and 4 000 Hz pure-tones were at a notably higher level than those to noise stimuli (approximately 81 dB SL). These threshold values indicate that it required about 20 dB of additional stimulation to obtain a response when pure tones rather than noise were used to elicit a stapedial response. The means for re-test thresholds are also shown in Table I. It can be seen that in all cases, except 250 Hz which was based on very limited data ($N=4$) the re test threshold was slightly lower than the initial threshold.

An examination of the standard deviations ociated with the mean stimuli thresholds ws that the standard deviations for the three noise stimuli are relatively homogeneous, the smallest being 4.42 and the largest being 5.56. The standard deviations for the pure tones are also relatively close to each other: the standard deviation for 2 000 Hz was 9.14 while the S.D. for 4 000 Hz was 8.81. The standard deviations for the pure-tones are significantly larger than those associated with the noise stimuli at the 0.01 level of confidence.

The data records for five random subjects were examined by two additional independent scorers. It was found that over 90% of each scorer's initial point of response judgments was within two decibels of the experimenter's judgment. All inter-scorer mean differences were found to be statistically insignificant. It is therefore concluded that the method of response recording used allows reliable inter scorer judgments of the threshold of the stapedius reflex.

CONCLUSIONS

The primary conclusion of this research is that the stapedius reflex is approximately 20 dB lower and significantly more stable, when elicited by noise rather than pure tones.

Table I. *Mean stapedius reflex thresholds (in dB SL) and associated standard deviations for both the test and re-test conditions for the six experimental stimuli*

	White noise	Narrow band 2k	Narrow band 4k	2k pure tone	4k pure tone	250 Hz pure tone
No. of subjects	30	29	30	29	15	4
Mean (test)	61.57	61.62	6..10	81.99	81.13	73.50
S.D	4.42	4.72	5.56	9.14	8.81	2.60
Mean (re-test)	60.57	60.31	61.57	80.69	80.87	73.50
S.D	5.24	6.24	5.55	8.51	8.52	2.96

The stapedius reflex thresholds for 2 000 and 4 000 Hz are in general concurrence with those presented by Metz and Jepsen, who utilized a different type of impedance bridge. The values found for white noise are 7 dB lower than those found by Lilly and 11 dB lower than those found by Dallos these reports were based on limited samples.

It should be noted that a small constant error may have affected the means for the stapedius thresholds. In some cases it was difficult to identify the first response of a series because the near threshold responses were relatively small. Consistently the more conservative (in other words, higher) response was chosen. The maximal effect this might have had on the threshold values obtained is estimated at 1–2 dB Should a system be designed to allow the measurement of smaller changes in the probe tone level, even smaller responses may be identifiable.

It was noted that the re-test thresholds were consistently lower than the initial determinations. This may be an example, in human ears, of the auditory sensitization phenomenon that Simmons (1960) found in the acoustic reflex in cats.

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ZUSAMMENFASSUNG

Die Zwislocki Akustikbrücke wurde angewandt, um den Stapediusreflex bei 30 normalen jungen Leuten zu untersuchen. Die benutzte Stimulierung war ein Spurt weißen Geräusches, in dem Bandspektrum von [illegible] 000 und 4 000 Hz, sowie sin-Töne von 250, [illegible] 000 und 4 000 Hz. Anstatt des gewöhnlich bei der Zwislocki Akustikbrücke benutzten Gehörmonitors wurde ein elektroakustisches Datenaufnahmesystem eingesetzt; die Empfindungsfähigkeit des Systems war solche daß sich Veränderungen von eins bis zwei dB in der Sondiertonstufe feststellen ließ. Die Durchschnittsschwelle der Werte der untersuchten sin-Töne waren 81 dB SL, während der Durchschnitt für die mit den verschiedenen Geräuschen verbundenen Stimuli 62 dB war. Es wurde beobachtet, daß die Schwellen der Geräusch-assoziierten Stimuli bedeutend beständiger waren, als die der sin-Töne.

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ACTION OF TUBOCURARINE AND ATROPINE ON THE CROSSED OLIVOCOCHLEAR BUNDLES

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Abstract The effect of atropine and *d*-tubocurarine chloride on the cochlear potentials and modification of the cochlear responses caused by electrical stimulation of the crossed olivocochlear bundles was examined in guinea pigs. Intravenous injection of gallamine triethiodide did not alter the inhibitory action of the crossed olivocochlear bundles. Section of the crossed olivocochlear bundles did not result in suppression of the cochlear microphonics. Perfusion of the scala tympani with Ringer s containing atropine or *d*-tubocurarine chloride did not alter the cochlear potentials but did block their responsiveness to the stimulation of the crossed olivocochlear bundles. The blocking activity of these anticholinergic drugs implies that acetylcholine is the possible transmitter of the crossed olivocochlear bundles.

The crossed olivocochlear bundles (COCB) described by Rasmussen (1946) have been extensively studied by anatomical and physiological methods. The sensory epithelium of the mammalian inner ear shows vesiculated nerve terminals in synaptic contact with the membrane of the hair cells (Wersäll, 1956 Engström 1958) The degeneration experiments clearly demonstrated that these vesiculated nerve endings belong to the efferent fibers (Kimura & Wersäll 1962) Electrical stimulation of efferent fibers suppresses the neural activity in the auditory nerve (Galambos, 1956 Fex, 1962 Sohmer 1966 Wiederhold & Kiang, 1970 Konishi & Slepian 1971 *a*)

Electron microscopic studies have revealed the presence of acetylcholinesterase on the presynaptic membrane of the efferent synapses on the hair cells (Hilding & Wersäll, 1962). However pharmacological studies showed diverse results. Tanaka & Katsuki (1966) failed to demonstrate the cholinergic nature of COCB, whereas recently Fex (1968) reported that the activity of COCB was suppressed by local introduction of *d* tubocurarine chloride into the cochlea of cats. It is likely that these diverse results are partially due to differences in experimental conditions or in administration of drugs.

In order to clarify the ambiguous data reported previously we undertook to examine the effect of anticholinergic drugs (*d*-tubocurarine chloride and atropine) on both the cochlear potentials and the inhibitory action of COCB when these drugs were introduced into the guinea pig cochlea. Our results show substantial suppression of the inhibitory action of COCB in response to the local application of these two drugs and provide favorable evidence to support the theory in conjunction with histochemical findings previously reported, that COCB belongs to the cholinergic fibers

METHODS

Healthy guinea pigs anesthetized with pentobarbital sodium (25 mg/kg body weight) were used throughout the experiments. A tracheotomy was carried out and the left jugular vein was cannulated for intravenous injection. The anesthesia was maintained at a level where the

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withdrawal reflex in response to pain was absent. The cochlear potentials were recorded from the basal turn of the right cochlea unless otherwise specified. The differential electrode technique was used for recording cochlear microphonics (CM) summating potential (SP) and whole-nerve action potential (AP) of the auditory nerve. The endocochlear potential (EP) was simultaneously recorded by a microcapillary electrode in the scala media of the basal turn. Details of the recording of the cochlear potentials have been fully described elsewhere (Tasaki et al., 1952 Konishi et al. 1961) The tone bursts used as acoustic stimuli were delivered in a closed system.

COCB was stimulated electrically in the floor of the fourth ventricle. The surgical exposure of the brainstem has been described in our previous paper (Konishi & Slepian, 1971 *a*) and was essentially the same as that used by Fex (1962). The stimulating electrode consisted of two enamel-coated stainless steel wires. The location of the stimulating electrode was adjusted along the midline of the brainstem at the level of the facial genu so as to obtain the maximum suppression of AP. The electrical stimuli to COCB were a train of repetitive shocks. The width of each shock was 0.3 msec and 40 shocks of 400/sec were delivered to COCB 10 msec prior to the onset of the tone burst.

The middle ear muscles were sectioned and the anesthetized animal was immobilized either with a transection of the spinal cord at the level of C_1 or an intravenous injection of gallamine triethiodide (1.0 mg/kg body weight). The experiments were carried out under artificial respiration. After the initial injection of gallamine, subsequent doses were reduced to half of the initial amount and administered approximately every 30 min.

The method of perfusion of scala tympani has also been described in our previous papers (Konishi et al., 1968) The rate of the perfusion was approximately 2 μl of the perfusate per minute. The Ringer solution had the following composition (mM): NaCl 137 KCl 5 $CaCl_2$ 2, NaH_2PO_4 1 $MgCl_2$ 1 $NaHCO_3$ 12, glucose 11 The pH of this Ringer solution ranged from 7.2 to 7.8 The *d*-tubocurarine chloride (Mann Research Laboratory) or atropine (Mann) was added to Ringer solution. The doses were expressed in molar concentration. The pH of these test solutions did not show significant difference from the pH of the Ringer's and therefore no adjustment of pH was made. The perfusate was kept at room temperature (20 C) In our preparations, except for a few the first perfusion was carried out with control Ringer solution for a period of 10 min. About 10 to 30 min later the test solution containing one of the above-described drugs was used as the second perfusate. The period of the second perfusion was the same as the first. The electrical responses were recorded periodically before during and after the perfusion.

RESULTS

In normal preparations, the electrical stimulation of COCB brings about not only modification of the sound-evoked responses to the tone bursts (augmentation of CM, inhibition of AP and modification of SP) but also evokes the d.c. potential in the scala media (COCP) as shown in Fig. 1 These changes in the cochlear potentials have been reported elsewhere in detail (Galambos, 1956 Fex, 1959 1967 *a*, *b* Konishi & Slepian, 1971 *a* *b*) In this report these documented phenomena were used to evaluate the drug action on COCB. The following approaches were employed for this purpose

1 *Effect of systemic introduction of gallamine on inhibitory action of COCB*

The anesthetized animals were immobilized by infrabulbar spinal transection and placed on artificial respiration. The input–output curves of CM and AP in response to 6 kHz were not affected by intravenous injection of 1.0 mg/kg of gallamine triethiodide. Also the isopotential curve of CM at 400 μV peak-to-peak in the range of 0.5 to 10.0 kHz was found to be with-

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ACTION OF TUBOCURARINE AND ATROPINE ON THE CROSSED OLIVOCOCHLEAR BUNDLES

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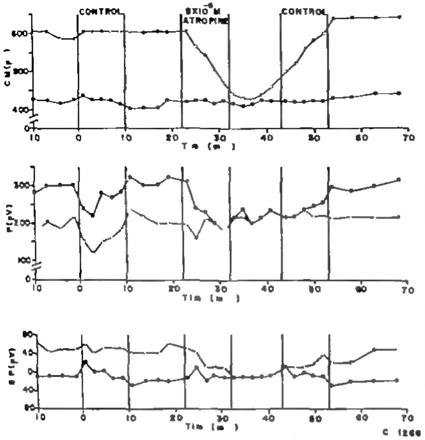

Fig 2 The influence of normal Ringer's and Ringer's containing 5×10^{-4} M atropine on CM, AP and SP and on modification of these responses by COCB stimulation, ● responses without COCB stimulation; ○ responses with COCB stimulation. Tone stimulus, 1 kHz tone burst at 40 dB above threshold for CM 6 kHz tone burst at 40 dB above AP threshold for AP and SP

AP was stable during a 2 hour observation period except during the initial period of perfusion. EP increased its magnitude by 5 mV but gradually returned to the original level during the perfusion. The input–output curves of CM and AP at [illegible] kHz showed essentially the same configuration before and after the perfusion. Also the isopotential curve of CM at the level of 400 μV was hardly affected by the perfusion and its difference fell within ±1 dB over the range of 0.5 to 10 kHz.

The perfusion of scala tympani with normal Ringer's did not abolish the responsiveness of CM SP or AP to the electrical stimulation of COCB (Fig. 2) In addition the magnitude or time course of the negative potential in the scala media evoked by COCP remained stable during and after the perfusion (Fig. 3)

4 *Action of atropine applied locally*

The concentration of atropine was varied from 5×10^{-6} to 5×10^{-4} M. With Ringer's containing atropine in this concentration range, CM and SP did not show a significantly different time course from those observed with the normal solution (Fig. 2). AP began to decrease during the initial stage of the perfusion in the same manner as that observed with the normal solution but did not recover during the perfusion. In the majority of cases, AP was suppressed during the entire period of the perfusion. When washing was performed with normal Ringer's, as shown in Fig. 2, AP showed a gradual recovery EP was little affected by atropine Ringer's applied into the scala tympani (Fig. 3).

The fact that with atropine-Ringer's in the scala tympani CM was not affected but AP was suppressed was demonstrated by measure

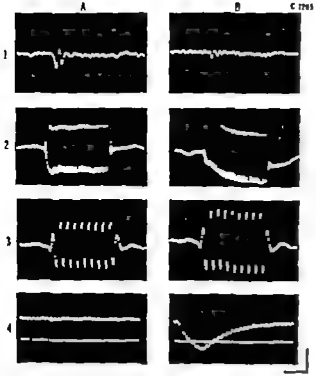

Fig 1 One example of the effects of electrical stimulation of the crossed olivocochlear bundles (COCB) on cochlear potentials. Column A without COCB stimulation B with COCB stimulation. Row 1 AP in response to 6 kHz tone burst at 30 dB above its threshold. Row 2: CM to 6 kHz tone burst at 50 dB above AP threshold Row 3 CM to 1 kHz tone burst at 30 dB above threshold. The upper trace in Row 4 shows the potential change in the scala media (COCP) and the bottom trace shows a marker indicating a trigger pulse for traces of CM and AP In each record, upward deflection is positive at input. Vertical scale at the right bottom corner is 200 μV for CM AP and 5 mV for d.c. potential change. Horizontal scale is 4 msec for CM and AP and 100 msec traces in Row 4 Parameters for COCB stimulation are as follows: 400 shocks/sec, 100 msec in duration of trains, 0.3 msec in shock width, 10 msec in interval between the trains of shocks and tone burst, and 100 μA in strength.

in the normal range of variation. After 1.0 mg/kg gallamine triethiodide was injected intravenously the effects of COCB stimulation on the cochlear potentials shown in Fig. 1 remained unchanged. The repeated systemic introduction of gallamine described in Methods over the period of 2 hours had no effect on the modification of the cochlear responses caused by COCB stimulation.

2 *Effect of section of COCB on cochlear responses*

The input–output curves of CM and AP to 6 kHz tone bursts were constructed by measurement of their magnitude on the oscilloscope. The error of readings was a function of signal to noise ratio. Even though the measurement of responses employed had limitation, there were no appreciable changes in the input-output curves of CM and AP that could be attributed with certainty to the surgical section of COCB at the midline of the brainstem in anesthetized animals immobilized either by gallamine or by infrabulbar spinal transection.

The isopotential curves of CM recorded both in the basal and the third turns were obtained by feeding CM into a wave analyzer The frequency of tones ranged from 0.5 to 10 kHz. The isopotential curves of CM at levels of 10, 50 and 100 μV rms were not modified either in the basal or third turn by the midline section of the brainstem. The section of the brainstem 3 mm away from the midline at the ipsilateral side did not alter CM recorded in either the basal or third turn.

3 *Control perfusion with normal Ringer's*

It has been shown in our previous papers (Konishi & Kelsey 1968 Konishi & Mendelsohn 1970) that the cochlear potentials did not change appreciably during the perfusion when normal Ringer's was introduced into the scala tympani at the rate of perfusion described in Methods. However the temperature of the fluid at the tip of the perfusion pipette was not monitored but it seems likely that it reached equilibrium with that of the cochlear fluid. Similar data have been reported by others (Moskovitz & Gannon 1966 Tasaki & Fernández, 1952) Specifically the variation of CM in response to 6 kHz tone bursts at about 80 dB SPL fell within ±15% of the preperfusion magnitude during perfusion and loss of CM was approximately 20 to 30% 2 hours after the perfusion started but did not show loss greater than 30% at the end of a 10 min perfusion (Fig. 2) In the majority of cases

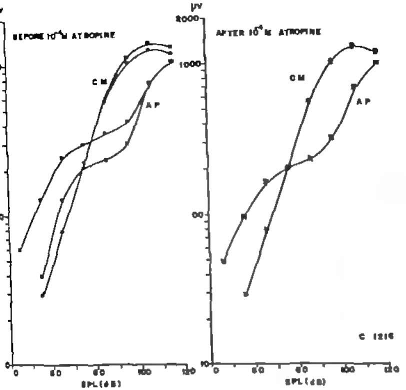

Fig. 4. Influence of 10^{-4} M atropine Ringer's on the input-output curves of CM and AP with or without COCB stimulation. Filled symbols, responses without COCB stimulation, open symbols, responses with COCB stimulation. Stimulus 6 kHz tone burst.

of COCB stimulation on CM or AP after introduction of 10^{-4} M atropine into the scala tympani. The isopotential curve of CM at the level of 400 μV was not modified by COCB stimulation in frequencies between 0.5 and 3 kHz. Fig. 6 shows the changes in SP with COCB stimulation before and after perfusion with 10^{-4} M atropine-Ringer's. It should be noted that atropine applied into the scala tympani suppressed the modification of SP caused by COCB stimulation.

5. *Action of d-tubocurarine chloride applied locally*

The concentration of *d*-tubocurarine chloride was varied from 10^{-6} to 10^{-3} M. With 10^{-6} M solution, about one-half of our preparations showed a clear effect on inhibitory action of COCB and 10^{-5} M solution resulted in abolition in all preparations. Fig. 7 shows one example of the action of 10^{-5} M *d*-tubocurarine on CM, EP and COCP. The CM in response to 1 kHz showed a slight increase in magnitude during the perfusion with the normal Ringer's, but the second perfusion with 10^{-5} M *d*-tubocurarine Ringer's did not affect the magnitude of CM. EP was not seriously affected by perfusion with either normal or *d*-tubocurarine solution. Changes in SP and AP in response to 6 kHz during the perfusion of 10^{-5} M *d*-tubocurarine were similar to those observed with the normal Ringer's (Fig. 8).

As shown in Fig. 7, the augmentation of CM by COCB stimulation was always observed during the control perfusion and the amount of its augmentation was stable except at the beginning of the perfusion. The augmentation of CM was abolished at the end of the perfusion with 10^{-5} M *d*-tubocurarine Ringer's. The COCP was entirely suppressed by *d*-tubocurarine-Ringer's applied to the scala tympani. The inhibition of AP caused by COCB stimulation was observed during and after the perfusion with normal solution and it was always accompanied by changes in SP. As illustrated in Fig. 8, the introduction of 10^{-5} M *d*-tubo-

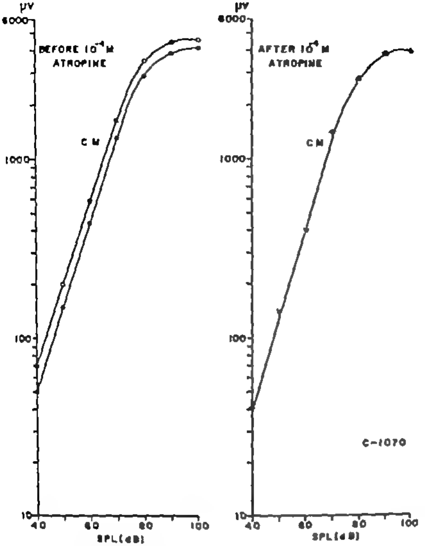

Fig 5 Effect of 10^{-4} M atropine on the input-output curve of CM with or without COCB stimulation. ● without COCB stimulation ○ with COCB stimulation Stimulus 1 kHz tone burst.

rine suppressed the inhibition of AP caused by COCB stimulation and the changes in SP were no longer observed at that time. Washing with control Ringer's resulted in the gradual recovery of responses to COCB stimulation.

The input-output curve of CM to 6 kHz was little affected after introduction of 10^{-3} M *d*-tubocurarine Ringer's. The input-output curve of AP indicated the suppression of AP in low intensity levels of sound stimuli after treatment with *d*-tubocurarine Ringer's. These changes in CM and AP were similar to those observed after the perfusion with atropine Ringer's However *d*-tubocurarine chloride Ringer's was effective in abolishing the modification of the input-output curves of CM AP and SP by COCB stimulation.

DISCUSSION

A series of criteria have been developed to identify a substance as a transmitter at a particular synapse The criteria which must be satisfied by any drug which is considered as a synaptic transmitter have been reviewed by Werman (1966) Paton (1958), Curtis (1961) and McLennan (1963). One of the most important criteria is that pharmacological agents which interact with the synaptically released transmitter should also interact with the suspected transmitter in an identical manner Other criteria include evidence to demonstrate the enzymic mechanism for the synthesis and inactivation of the presumed transmitter There-fore several essential criteria remain to be tested in order to identify the transmitter re-

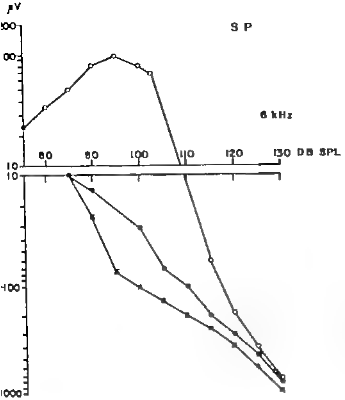

Fig 6 Effect of 10^{-4} M atropine on the input-output curve of SP with or without COCB stimulation. ○ ● SP with and without COCB stimulation respectively before application of atropine. □ ▲ SP with and without COCB stimulation respectively after application of atropine.

leased at the hair-cell efferent synapses. To date several investigators have tested the action of atropine or *d*-tubocurarine chloride on the COCB. Atropine specifically blocks the action of acetylcholine at muscarinic synapses and *d*-tubocurarine chloride blocks the action of acetylcholine at nicotinic synapses. The previous results did not show consistent effects of these two drugs on the COCB. Several factors must be considered to explain the previous diverse results. Our data seem to indicate that the discrepancy of the previous reports is due to the different methods used to administer the drugs and to the fact that different criteria were used to assess the effect of these drugs on the cochlear potentials i.e. measurements of cochlear potentials with or without COCB stimulation.

Gallamine triethiodide is a synthetic, curare like compound and its chief pharmacological action is to produce a blockade of neuromuscular transmission but it exhibits no known action on autonomic ganglia, thus differing from *d*-tubocurarine. Brown et al. (1969) reported that intravenous injections of 2.0 mg/kg of gallamine did not affect either CM or AP in cats. Guth & Amaro (1969) reported that atropine (0.5–5 mg/kg) or *d*-tubocurarine (2 mg/kg) did not antagonize COCB-induced inhibition, when these drugs were injected via a cannula in the axillary artery. Sohmer & Feinmesser (1963) also reported the absence of response to systemically injected atropine (20 mg) upon the SP inhibition caused by COCB stimulation. In order to account for the difference of drug action between systemic and local administration, it appears that gallamine or atropine does not diffuse through the blood–cochlear barrier. Pharmacological and physiological evidence has not been reported concerning the existence of blood–cochlear barrier. Similar results have been recently reported by Galley et al. (1971). It should be emphasized that the action of drugs can be more critically

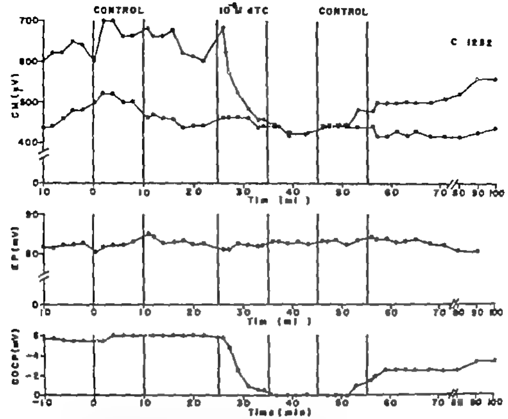

Fig 7 Effect of perfusion of scala tympani with 10^{-6} M *d*-tubocurarine chloride Ringer's on CM, EP and COCP In uppermost panel, ● CM without COCB stimulation, ○ CM with COCB stimulation. Stimulus for CM, 1 kHz tone burst at 30 dB above threshold.

evaluated by their local application into the cochlea than by systemic injection.

Rossi et al. (1964) observed that section of COCB at the midline of the brainstem resulted in suppression of CM in guinea pigs. This result implies that the AP is tonically suppressed by the activity of COCB On the basis of this implication several investigators expected that changes of CM or AP would be produced by modification of tonic activity of COCB with drugs introduced into the cochlea. Johnstone (1965) perfused the perilymphatic space with *d*-tubocurarine, physostigmine and acetylcholine and found that AP did not change after local application of physostigmine. Also Sohmer & Feinmesser (1963) reported absence to responses to AP to atropine and eserine, when they were applied into the cochlea. Thus these investigators concluded that the absence of response to atropine and eserine applied to the cochlea does not support the hypothesis of a cholinergic mechanism for COCB. As described in Results, we confirmed the fact that changes in CM or AP after local introduction of atropine or *d*-tubocurarine were found to be within the range of variation of those responses observed in the control perfusion. However we interpret this finding differently First, the section of COCB did not result in suppression of CM and potentiation of AP as evidenced by the input–output curves at 6 kHz In addition this was confirmed by the fact that CM both in the basal and the third turns remained unaltered after the section of COCB It has been reported that the distribution of COCB fibers is greater in the basal turn than in the third turn (Teas et al., in press Ishii & Balogh, 1968) Should the section of C affect CM, CM would be more reduced in the basal turn than in the third turn. As this is not

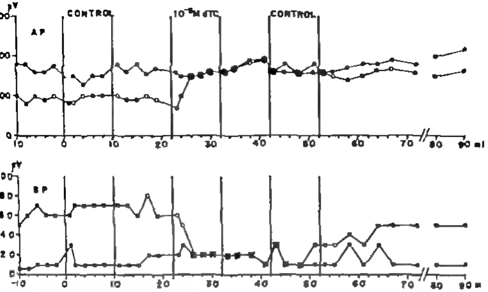

Fig. 8. Effect of perfusion of scala tympani with 10^{-5} M *d*-tubocurarine chloride Ringer's on AP and SP. Filled symbols, responses without COCB stimulation, Open symbols, responses with COCB stimulation. Stimulus 6 kHz tone bursts at 40 dB above AP threshold.

the case, this casts doubt on the theoretical assumption that AP is being tonically suppressed by COCB activity. Thus it is not legitimate to rule out the possibility of cholinergic mechanism of COCB from the fact that the perfusion with the anticholinergic drugs did not modify CM and AP without COCB stimulation.

The effects of *d*-tubocurarine on the inhibitory action of COCB have been studied by Tanaka & Katsuki (1966) and Fex (1968) when *d*-tubocurarine was introduced into the cochlea. Tanaka & Katsuki reported that *d*-tubocurarine iontophoretically applied near the hair cells had no effect on the inhibition of AP produced by COCB stimulation in cats. On the other hand, Fex demonstrated the clear blocking effect of *d*-tubocurarine on the inhibitory action of COCB by employing the technique of perfusing the scala tympani in cats. Our methods and results are in line with those reported by Fex and the effective doses used by us are equivalent to those of Fex. As the dose of *d* tubocurarine iontophoretically injected was not reported by Tanaka & Katsuki, it is difficult to compare our data with their results. Recently Russell (1971) described the effect of atropine and *d*-tubocurarine chloride on the efferent inhibition of the lateral-line receptors in *Xenopus* and *Acerina*. His results clearly indicate that the inhibition of spontaneous afferent impulses, caused by electric stimulation of efferent fibers or by bathing the receptor in low concentrations of acetylcholine, is blocked by low concentrations of atropine (5×10^{-6} M) or *d*-tubocurarine (5×10^{-5} M). He argued that, in the concentrations used, atropine and acetylcholine were not acting non-specifically on the lateral-line receptors and supported the hypothesis that acetylcholine is released at lateral-line efferent synapses.

The blockade of the inhibition of AP induced by COCB stimulation can be attributed to one or several of the following actions. The conduction of the nonmyelinated portion of the COCB may be blocked, resulting in ineffectiveness of electrical stimulation of COCB. The excitability of the hair-cell membrane may be reduced. Thirdly *d*-tubocurarine chloride or atropine may act on specific receptor sites at the efferent synapses and interfere with the cholinergic mechanism of these synapses. The

compound action potential elicited from the mammalian unmyelinated fibers was not suppressed either by 10^{-4} g/ml^{-1} of atropine or 10^{-2} g/ml^{-1} of *d*-tubocurarine chloride (Arnett & Ritchie, 1961) Complete blockade of the inhibitory action of COCB was observed by perfusing the scala tympani with Ringer's containing 10^{-5} M *d*-tubocurarine chloride (8×10^{-7} g/ml^{-1}) or 5×10^{-3} M atropine (1.5×10^{-8} g/ml^{-1}) These concentrations are much less than those necessary to produce changes in conduction in unmyelinated nerve fibers. Also it is unlikely that atropine or *d* tubocurarine chloride in the concentration used alters the excitability of the hair-cell membrane. The significant changes in CM should be observed without COCB stimulation when one of these drugs is locally applied into the cochlea. Thus it seems conceivable to suppose that *d* tubocurarine chloride or atropine interferes specifically with the synaptic transmitter of the COCB

The above mentioned hypothesis has been strengthened by recent work of *Bobbin & Konishi* (1971) They found that perfusion of the scala tympani with Ringer's containing 2.5×10^{-4} M acetylcholine and 10^{-5} M eserine sulfate resulted in an augmentation of CM, inhibition of AP and blockade of the effects of COCB stimulation. The question of whether ...choline when extraneously applied ... the action of synaptically released transmitter has not been answered by the present literature (Gisselson, 1960 Tanaka & Katuski, 1966). It can be interpreted from our findings that the post-synaptic events which are brought about by electrical stimulation of COCB are similar to those observed after the external application of acetylcholine

One other aspect discussed is the possibility of interference with the inner ear blood circulation by the anticholinergic drugs. Ishii (1971) demonstrated that the diffuse acetylcholinesterase activity was present in the vascular wall of the stria vascularis and spiral ligament but no neural structures were discerned. From these findings he postulated that the neurogenic control of the blood vessels in the inner ear is not directly exerted in the arteries of the labyrinth. Neither atropine in concentration of 5×10^{-3} M nor *d*-tubocurarine of 10^{-4} M reduced CM and EP It is unlikely that in the concentrations used, atropine or *d*-tubocurarine chloride was acting non-specifically on the blood circulation.

Several other criteria remain to be tested before acetylcholine is accepted as a synaptic transmitter of COCB However our findings, in conjunction with the mimicking action of externally applied acetylcholine and the presence of acetylcholinesterase in COCB, provide evidence that COCB is of a cholinergic nature.

RESUMÉ

L'effet de l'atropine et de la chlorure de D-Tubocurarine sur les potentiels de la cochlée et les modifications des réponses cochléaires causé par la stimulation électrique du faisceau olivo-cochléaire croisé, été experimenté sur les cobayes. L'injection intraveineuse du *gallamine triethiodide* n'a pas changé l'action inhibiteur du faisceau olivo-cochléaire croisé. Section du faisceau olivo-cochléaire croisé ne resulte pas en suppression des microphoniques
Perfusion de la rampe tympanique avec la solution Ringer contenant atropine ou chlorure de D-T curarine n a pas changé les potentiels cochléaires mais bloc leur sensibilité au stimulation de faisceau olivo-cochléaire croisé. L'activité bloquante de drogues anticholinérgiques implique que l choline est le transmetteur possible des olivo-cochléaire croisés.

ZUSAMMENFASSUNG

Der Einfluss von Atropin und d-Tubocu auf die elektrischen Potentiale der Schnecke und durch diese Drogen hervorgerufenen Veränderungen in dem Verhalten der Schnecke auf elektrische Reizung der gekreuzten olivocochlearen Bündel am Meerschweinchen untersucht. Intravenöse Inj von Gallamintriethiodid änderte die der gekreuzten olivocochlearen Bündel nicht. trennung der gekreuzten olivocochlearen Bündel führte zu keiner Unterdrückung der cochlearen MP Durchspülen der Scala tympani mit Ringerscher L sung, die Atropin oder d Tubocurarinchlorid hielt, verursachte keine Veränderung der Po der Schnecke, blockierte aber die Ansprechbarkeit Potentiale auf Reizung der gekreuzten oli Bündel. Der Hemmeffekt dieser anticholinergisch

Stoffe bedeutet, dass in Acetylcholin der mögliche Überträgerstoff der gekreuzten olivocochlearen Bündel zu sehen ist.

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AN ELECTROMYOGRAPHIC ANALYSIS OF IDIOPATHIC VOCAL CORD PARESIS

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Abstract. Ten patients with idiopathic vocal cord paresis were subjected to electromyographic examination. By means of a transcutaneous approach, some 20 motor unit potentials from each vocal muscle were identified. The electromyographic pattern showed great interindividual differences. In all patients investigated it differed from the normal pattern in a way indicating a neurogenic lesion. In all muscles investigated there were changes showing that part of the motor units of the vocal muscle was subjected to denervation.

The underlying cause of vocal cord paresis cannot be determined in about one third of the cases (New & Childrey 1932 Clerf 1953 Williams, 1959) Since in several of these though not all, an acute upper respiratory or constitutional infectious process has preceded the voice disturbances, it has been suggested that the paresis is due to a neuritis of the recurrent laryngeal nerve of either of the following categories: infectious, toxic and angiospastic (Faaborg-Andersen, 1954). Also, mechanical injury to the inferior laryngeal nerve has been suggested as causative, a compression of the nerve arising when it passes the cricothyroid joint and thus giving rise to blockage of impulse transmission (Ogura, 1961) If the onset of symptoms is acute a neurogenic lesion seems probable, but when insidious, a myogenic etiology must also be considered.

Several reports of electromyographic recordings from vocal muscles in idiopathic vocal cord paresis have been published (Faaborg-Andersen, 1957 Hiroto et al. 1968 Dedo, 1970) However due to the uncertainty inherited in analysis from an insignificant number of potentials as well as to the lack of data on the distribution of duration, amplitude and shapes of the potentials recorded in normal muscles, it has not been possible to describe the deviations observed with sufficient precision to draw any conclusions concerning the etiology of the paresis. The method for electromyographic examination of the vocal muscle by means of a transcutaneous approach under surface anesthesia of the subglottic mucosa used in an analysis of the normal electromyogram in vocal muscles (Knutsson et al., 1969) usually permits identification of a sufficient number of potentials to allow an estimation of the significance of an altered incidence of potentials of certain types (Haglund et al. 1970).

Hence, this method has been used in an electromyographic analysis of the vocal muscle in a series of patients with idiopathic vocal cord paresis. From the results, it will be apparent that the electromyographic pattern was highly various though in each case dif

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Table I. *Electromyographic data from vocal muscles in idiopathic vocal cord paresis*

In the different columns are given time of recovery after onset of symptoms of paresis, time of the electromyographic examination after onset, mean duration and dispersion of sample of potentials in each muscle, relative number of potentials with a duration of 2 msec or less, an amplitude of 0.15 mV or less, an amplitude equal to or larger than 0.70 mV as well as of potentials with five or more phases. The interference pattern is given as normal, incomplete or none. Corresponding data from normal muscles in brackets.

Case	Time of recovery (months)	EMG time after onset (months)	n	Duration: Mean and S.D. msec (3.76±1.01)	Duration: <2 msec (0–15 %)	Amplitude: ≤0.15 mV % (10 %)	Amplitude: ≥0.70 mV % (10 %)	Polyphasic (0–15)	Interference pattern
1. H. G.	7	2	—	—	—	—	—	—	Incomplete
		5	13	5.19±2.80	11	56	15	46	Incomplete
2. G. J.	10	6	22	4.25±2.72	36	46	5	9	Incomplete
		8	17	3.53±1.22	18	18	12	18	Normal
3. S. O.	4	2	21	4.45±2.15	10	24	19	19	Incomplete
		4	18	3.50±1.33	13	19	19	25	Incomplete
4. G. P.	7	4.5	16	5.94±1.14	0	0	75	0	Normal
5. Ö. W.	1.2	0.8	22	2.72±1.19	50	64	8	0	Incomplete
6. K. O.	4.5	2.5	26	4.83±1.15	0	8	70	0	Incomplete
7. G. A.	nil (2 years)	1	—	—	—	—	—	—	None
		2	10	2.63±1.10	50	90	0	0	None
8. M. L.	nil (1.5 years)	4	17	4.94±2.14	12	29	23	41	None
9. K. K.	nil (12 years)	120	31	4.53±1.21	6	10	35	17	None
10. T. L.	nil (2 years)	24	15	6.87±2.12	0	6	60	0	Incomplete

potentials of short duration. In spite of this fact, it seems perfectly relevant to draw the conclusion that fibrillation potentials were present in cases 5 and 7 on the basis of increased incidence of short potentials of low amplitude. In case 7 only one of the potentials observed appeared during a respiratory phase or during deglutition and phonation. Consequently only this potential could be classified as a true motor unit potential. All the others might well have been fibrillation potentials but the proportion between denervation potentials and motor unit potentials cannot be determined with exactitude.

Increased mean duration of the potentials

In 5 patients (cases 1, 4, 6, 8 and 10) the mean duration of potentials recorded was significantly increased. Fig. 2 shows distributions of the durations and amplitudes of the potentials identified in one of these (case 4) in which there was an increased incidence of potentials with high amplitudes and long duration. Very similar tendencies were observed in cases 6 and 10. Thus a large incidence of potentials with increased duration was present in these cases. The potentials had two or three phases and were of relatively high amplitude. This pattern is consistent with a neurogenic lesion.

In the other 2 cases with increased mean duration of the potentials (cases 1 and 8) about

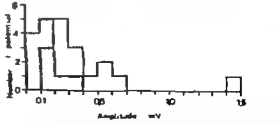

Fig. 1. Amplitude distribution of potentials of a duration of 2 msec or less recorded from vocal muscle in Case 5 (hatched columns) as compared with corresponding data from the normal material (blank columns).

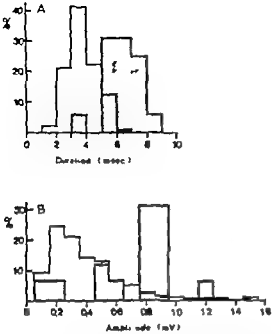

Fig 2 Duration and amplitude distribution of potentials recorded from vocal muscle in Case 4 (hatched columns) as compared with corresponding data from the normal material (blank columns).

half of the potentials showed significantly in creased duration, and these were practically all polyphasic and with amplitudes of between 100 and 1 000 μV The incidence of potentials shorter than 2 msec was not greater in any of the muscles than in normal muscles. Thus, ... was no evidence for the presence of ...ation potentials although their existence cannot be completely ruled out. During deglutition and phonation there was an incomplete interference pattern in 4 cases and an absence of interference in 1 These findings together with the large proportion of potentials with increased duration indicate the presence of neurogenic injuries.

Normal mean duration of potentials

Mean duration within normal limits was observed in 3 patients (cases 2, 3 and 9). Distri bution curves for durations and amplitudes of the potentials recorded in the examination of patient 2 on the occasion of the first investigation are shown in Fig. 3 It is seen from the histogram that the incidence of potentials with relatively long duration as well as of short duration was increased. The short potentials had usually an amplitude lower than 150 μV which suggests fibrillation potentials. *Amongst potentials with increased duration* were often seen polyphasic potentials. All these had a relatively low amplitude (range 100–350 μV), i.e. nascent units.

In the other 2 cases with normal mean duration the pattern was entirely different. In case 3 the motor unit potentials were, as a rule, of normal duration and amplitude, but the interference pattern was incomplete, and *a few polyphasic potentials of high amplitude* (range 1 200–2 800 μV) and long duration (range 5–10 msec) were observed. As can be seen from the table, a large proportion of the potentials identified in case 9 were of a large amplitude. Among these, six potentials had an amplitude in the range 1–4 mV and durations of about 5 msec and hence, might be regarded as giant potentuals. There was no interference pattern during activation by swallowing or phonation, the activity being charac

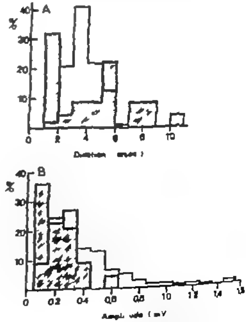

Fig 3 Duration and amplitude distribution of potentials recorded from vocal muscle in Case ... (hatched columns) as compared with corresponding data from the normal material (blank columns).

terized by single oscillations of high amplitude.

Changes in the EMG during healing

In 4 patients two recordings were made on different occasions during the course of the paresis. In two of these, no action potentials could be identified at the first recording. In one (case 1) swallowing and phonation gave rise to some activity though no full interference. In the other (case 7), only activity from distant muscles could be observed. On a second examination, 1 to 3 months later fibrillation potentials were observed in both cases. This indicates that fibrillation potentials may appear relatively late after the onset of vocal cord paresis. In the other two in whom repeated examinations were made (cases 2 and 3), it was established that the mean duration and its dispersion decreased, which agrees with the successive shortening of the duration of the motor unit potentials observed in cats during reinnervation (Golseth & Fizzell, 1947).

In cases 1–6 the paresis was healed after 5 weeks and up to 10 months, as revealed by frequent indirect laryngoscopic examinations. As criterion of healing, a normal voice and normal movements of the vocal cords on intonation and during quiet breathing was used. In all these cases there was evidence from the electromyographic examination of a reinnervation prior to return of movements. In cases 7–10 paresis has been sustained for 1–2 years after the last electromyographic examination.

DISCUSSION

In only three of the paretic muscles examined was direct evidence of denervation by the presence of fibrillation potentials obtained. In the remainder the incidence of short potentials did not differ significantly from the incidence in normal muscles. Since motor units in the healthy vocal muscle are repeatedly activated despite every effort to obtain relaxation, motor unit potentials could not be distinguished from possible fibrillation potentials in these cases. Also in those cases in which fibrillation potentials could not be demonstrated, there was evidence supporting a prior nerve injury. In these cases different signs of reinnervation were found similar to those observed after traumatic recurrent nerve paresis (Haglund et al. 1970) i.e. an increased incidence of potentials with long duration, of high amplitude and/or with more than four phases (cf. Golseth & Fizzell, 1947; Yahr et al., 1970; Buchthal & Pinelli, 1953; Erminio et al. 1959).

The EMG records from vocal muscles during reinnervation (Faaborg Andersen, 1957; Hiroto et al. 1968; Dedo, 1970) show patterns similar to those found in other muscles. However, in two of the patients subjected to repeated EMG examinations a higher incidence of polyphasic potentials with long duration was found early during reinnervation, than during late stages of healing, when the duration of the potentials and their number of phases became more congruent with those of normal vocal muscles. A similar normalization of duration and shapes of action potentials has previously been observed in EMG recordings from the anterior tibial muscle of the cat during reinnervation after section and suture of the sciatic nerve (Golseth & Fizzell, 1947). This has also been apparent in vocal muscles during healing after traumatic paresis of the recurrent laryngeal nerve (Haglund, Knutsson & Mårtensson, unpublished data). It has been proposed that such changes occur in other muscles during reinnervation (Woolf 1962), but in clinical electromyography their presence does not seem to have been taken into consideration to any great extent.

The long duration of the potentials early during healing in idiopathic vocal cord paresis most probably depends upon an increased temporal dispersion of the neuromuscular transmission, and the consequent variation in time of arrival at the recording electrode of the propagated action potentials in different muscle fibres. Other factors of significance appear to be a low conduction velocity in

somatosensory deprivation or disturbed somesthetic feedback control of the speech motor activity of the lips. Some of the results have been presented in preliminary reports (Leanderson & Persson, 1971 Persson & Leanderson, 1971)

METHODS

The EMG of facial muscles during speech was investigated in 10 adult volunteers (7 female and 3 male) with clinically normal speech without and with uni or bilateral mandibular anaesthesia (Xylocain 2%) which was administered by an oral surgeon. Further more 6 patients (2 female and 4 male) with trigeminal neuralgia were investigated before and after an alcohol injection in the Gasserian ganglion, performed as treatment by a neurosurgeon The anaesthetic effect was controlled by light touch, pin prick and testing of the perioral reflex (Ekbom et al., 1952 Kugelberg, 1952) In the subjects the sense of touch and pain was eliminated from the mucous membrane of the anterior two-thirds of the tongue the inside of the cheek and lower lip and the skin of the lower lip and chin. The reflex response from M. orb oris inf either disappeared or was (in 1 subject) markedly delayed, reflecting a reduced afferent conduction rate In the patients the anaesthetic effect was observed also in the upper lip, and the reflex response disappeared even from M orb oris sup Concentric needle electrodes were used for EMG recording in all experiments. The experimental procedure and data processing have been described in an earlier publication (Leanderson et al., 1971). In the experiments with anaesthesia, special care was taken to keep the electrodes in the same position through the experiment.

In the subjects, M orb oris inf and M dep lab were investigated bilaterally In the patients, M lev lab., M orb oris sup., M orb oris inf and M dep lab were investigated on the side to be operated on these investigations were performed the day before and the day after the operation.

The subjects and patients were all familiar with the phonetic test material before the first recording and reported no discomfort from the needles when the actual experiment started. Three readings of randomly mixed VCV utterances were recorded and analysed with and without anaesthesia and before and after operation respectively Only utterances with an acoustically correct pronunciation were analysed.

RESULTS

An earlier study (Leanderson et al., 1971) has shown that the EMG activity from the lip muscles during speech can be separated into two functionally different activities: a background or speech posture activity and an articulatory activity associated with the articulatory movements proper This distinction will be observed in the following account.

Background activity

Fig. 1 shows the effect of bilateral mandibular anaesthesia on the activity in M. orb. oris inf and M. dep. lab. bilat. The resting activity between utterances was usually much the same. Very often a marked increase was observed at the beginning of an utterance as shown in the figure, a rather strong symmetrical activity of quite long duration appeared even though without anaesthesia the spread vowels of the first acoustic segment, [ɛ] and [a] in [ɛja], do not demand very much labial activity This prespeech activity which started in some subjects several hundred msec before one would expect the proper articulatory activity for the first speech sound, is to be regarded as speech initiation activity (MacNeilage, 1970 Leanderson & Lindblom, 1972). In other experiments the background activity before anaesthesia was increased by having the subject smile during the utterances and by changing the initial word of the contextual frame from /sɛja/ to /syna/ The speech initiation activity was then not only stronger but also started earlier compared with the experiments

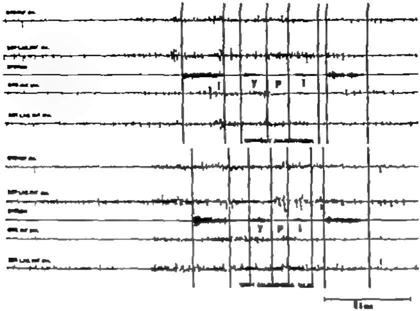

Fig. 1. EMG recordings of /ypı/ utterances showing the increase of pre speech activity in M. dep. lab bilat. with anaesthesia.

which the subjects relaxed between utterances. With anaesthesia, however the onset time of the prespeech activity was shorter than before anaesthesia and of the same order of magnitude as in the experiments with smaller background activity. It was a general observation that the intra and interindividual variability in the anticipation period of prespeech activity (Leanderson & Lindblom 1972) was smaller with anaesthesia.

Articulatory activity

The most salient finding with mandibular anaesthesia was usually a marked general in-

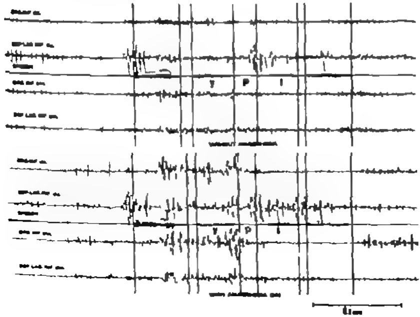

Fig. 2. Increase of articulatory EMG activity on both sides with unilateral mandibular anaesthesia.

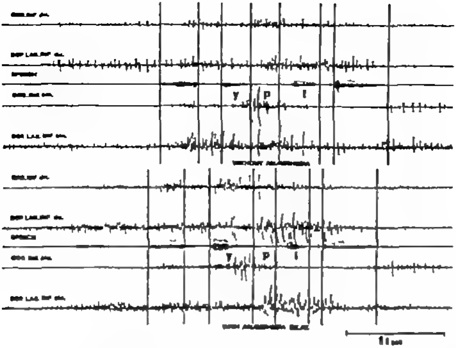

Fig. 3. Decrease of EMG activity in M. dep. lab. sin. for the production of [y] with mandibular anaesthesia.

crease in the proper articulatory activity (Fig. 2). This increase was noted in all the subjects and it waned as the anaesthesia weakened. It was not possible to determine which sensory quality was most important for the observed effect of anaesthesia on the articulatory activity. However, complete block of the afferents that mediate the early perioral reflex for a light tap was not necessary to produce the observed effect. On the other hand, surface anaesthesia of the oral mucosa (Xylocain 4%) had no effect on the EMG pattern.

The increase in activity after nerve block was not restricted to the muscles innervated by the nerve in question. During anaesthesia of the mandibular nerve, increased activity was usually seen in M. lev. lab. and M. orb. oris sup. as well. Furthermore, increased EMG activity was mostly observed bilaterally even when anaesthesia was unilateral. These findings are hardly compatible with a disturbed peripheral closed loop feedback mechanism as a cause of the increased motor unit activity after nerve block.

The increased activity with mandibular anaesthesia was most pronounced in those muscles which are best adapted for the production of the vowels and consonants involved, that is to say M. orb. oris inf. for lip-rounding/closing and M. dep. lab. for lip-opening/spreading gestures.

With anaesthesia, inadequate activity often decreased or disappeared. Such an example is shown in Fig. 3. Before anaesthesia the subject had a prominent burst of activity in M. dep. lab. sin. for the lip-rounding gesture for [y]. This inappropriate activity de... with anaesthesia. The activity in antago... nistic muscles, which may be qu... during contractions against small resistance (cf. Wilkie, 1950; Barnett & Harding, 1955) sometimes showed a slight ... but often remained unchanged or even dimin... ished. This phenomenon was best observed during the activity of longer duration associated with a vowel compared with the shorter ... tivity for a stop consonant.

Any change of the articulatory activity ... anaesthesia was, as a rule, equally pron... for vowels and consonants. Increased activity was often associated with an earlier onset of the activity but the difference in anticipatory time between vowels and consonants ... preserved.

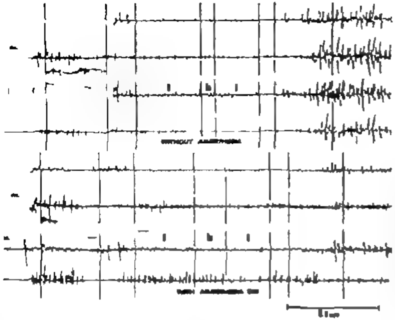

Fig. 4. Impaired context dependence of the EMG activity. For each spread acoustic segment new activity appears in M. dep. lab. particularly on the anaesthetized side (cf. the record above from the same muscle without anaesthesia).

xt dependence

ally the degree of motor unit activity in cle used for the production of a certain ı sound was found to be strongly de nt on how much that muscle had been during the preceding sound (Leander al., 1971). This applies to consonants as to vowels. In view of the debatable of context dependence in normal speech (e.g. Öhman, 1967; Mac ., 1970; Ringel, 1970) it was of interest whether mandibular anaesthesia had on this phenomenon. Fig. 4 shows G in M. orb oris inf. and M. dep. lab. [ihi] before and after nerve block on side. Unlike the case before an- sia, a new burst of activity appeared nerve block for each similar spread tic segment (s[ɛja], [i]₁, [i]₂ and d[arɛ]) hange was most pronounced on the an- tized side but it also appeared on the side. No such effect was detected, on the hand, in the case of context dependence nsonants, e.g. the activity for [p] starting after [i] than after [u]. Thus, peripheral ck from the involved facial region is not tely necessary for the phenomenon of context dependence in adult speech, but may be of some importance for the production of vowels.

DISCUSSION

In the present study total or partial blocking of the afferent activity in the mandibular nerve or the Gasserian ganglion produced consistent changes in the EMG activity of facial muscles during speech, the most prominent finding being increases in prespeech, background and articulatory activity. Individual differences in the degree and type of change in the EMG pattern were found among subjects and patients but no systematic differences were seen between the two groups. The differences between subjects corresponded to those described previously for normal undisturbed articulation (Leanderson & Lindblom, 1972). In all cases the EMG pattern with anaesthesia differed from that without.

As in earlier studies of normal speech (Leanderson et al., 1971), the EMG pattern for a particular utterance with anaesthesia displayed good reproducibility. Changes of the same type were obtained for a particular sub-

ject who was anaesthetized on several occa sions. Bilateral mandibular anaesthesia has been used before in speech research by Mc-Croskey (1958) and Ringel & Steer (1963) whose listener tests revealed significant arti culatory inaccuracy under the influence of an aesthesia. The absence of any audible changes in the articulation in the present study may reflect differences between the phonetic test materials Like Ringel & Steer (1963) we found that the speech remained highly intelli gible with anaesthesia

No studies have been published before concerning the EMG activity of lip muscles dur ing speech with anaesthesia The effectiveness of the nerve block was tested by means of the perioral reflex response. The afferent part of this reflex pathway runs in the trigeminal nerve (Ekbom et al. 1952 Rushworth, 1962 Bynke, 1971) As a rule the response disappeared 3 to 5 minutes after the anaesthetic had been injected. Even though the nature of the facial reflexes has been much discussed lately and may be elicited by the stimulation of exteroceptive skin receptors (Lindquist & Mårtensson 1970 Shahani, 1970) the elimina tion of such reflexes must mean that all af ferent fibres of the trigeminal nerve are blocked which can conceivably be of any importance for a peripheral closed-loop feedback. There are also afferent fibres in the facial nerve (Brodal, 1966) but so few that they are probably of minor importance for the type of feedback discussed here

As to the possibility of other changes connected with the experiment having brought about the effects on the EMG activity during mandibular anaesthesia, it must be remem bered that the appearance and disappearance of these effects coincided with the anaesthesia and that the effects were entirely reversible Nor could similar changes be elicited by other means, such as altering the position of the mandible

Which types of receptors are most important for the integration of normal articulatory EMG patterns of the lip muscles? Anaesthesia of the oral mucosa did not elicit EMG changes. Muscle spindles are very sparse, if not non-existent, in the facial muscles in man (Kadanoff 1956 Filogamo quoted by Gandiglio & Fra, 1967) as they are in cat (Lindquist & Mårtensson, 1970) nor would they be of any particular functional significance in the peri-oral muscles in view of the topographic anatomy the various muscles being interwoven as a composite unit, often in anatomic contiguity with the skin, and the largely isotonic nature of the contractions. However suspension of positional sense might explain the disturbed context dependence of the EMG activity demonstrated in the experiments and illustrated in Fig. 4 This indicates the probability that receptors other than muscle spindles provide afferent information for the proper function of the mimic muscles. Intradermal and/or intramuscular receptors, possibly free nerve endings, which have been observed in large numbers in labial muscles (Kadanoff, 1956) are presumably stimulated when the early discharge of the facial reflex is elicited (Lindquist & Mårtensson, 1970; Shahani, 1970)

Increased activity prespeech and background as well as articulatory was an unexpected finding during blocking of afferent fibres because de-afferentation leads to reduced voluntary and reflex motor unit activity in man (Nathan & Sears, 1960) as well as in cat (Sears, 1964) The apparent contradiction may well be resolved by differences in the organization of the motor systems of labial as opposed to limb muscles, the former probably lacking muscle spindles (cf above) and gamma efferents. The fibre spectrum of the facial nerve in man contains very few thin efferents that might constitute gamma fibres (Buskirk 1945)

The increased muscular activity when the afferent inflow is blocked can be explained in terms of the muscle control now being exercised from a "higher" level in the central nervous system without the participation of "subconscious" mechanisms that normally

tion in speech production. A similar com-
atory activity after de-afferentation has
observed with other types of skilled
ements (Knapp et al., 1963 Konorski,
). A greater element of "conscious" ac
may also explain other findings during
dibular anaesthesia. bilateral changes when
sthesia is only unilateral, and a stronger
eech activity with a less variable onset

ie importance of a peripheral closed-loop
back operating the articulatory muscles
g connected speech has been discussed
y (e.g. Hardy 1970 Ringel, 1970) and its
ence has been claimed by some authors
the basis of experimental observations
an, 1967 MacNeilage, 1970· Abbs, 1971)
present study has not yielded evidence of
ripheral closed-loop feedback as a pre
isite for the motor control of articulatory
ity in labial muscles. None of the changes
rved during anaesthesia can be attributed
ly to a disturbance of such a supposed
ack. If such a feedback were operating,
would expect to find, for instance, that
normal context dependence of EMG ac
for consonants in relation to the identity
a pre-consonantal vowel (Leanderson &
blom, 1972) were impaired or missing.
is there any anatomical basis for a feed-
mechanism in the labial muscles of the
type as in the limb muscles.
though there is little evidence to support
ripheral closed-loop feedback in speech,
present results show that blocking of af
t activity from the labial muscles elicits
bvious change in the EMG activity pat
for different speech gestures The soma
sory feedback suggested by these find-
does not appear to be of fundamental
ortance for articulatory motor control in
t normal-speakers. That it may be essen
for the normal process of articulatory
sition in childhood is suggested by the
ngs of MacNeilage et al. (1967) concerning
tient with impaired somesthetic sensation
early childhood, probably congenital,
that had resulted in severe deficiency in speech production

ZUSAMMENFASSUNG

Die Auswirkung einer Blockierung der afferenten Fasern des Trigeminus auf die EMG-Aktivität der Lippenmuskeln während des Sprachproduktionsprozesses wurde des näheren untersucht. Das Untersuchungsmaterial bestand aus normalsprechenden Versuchspersonen, deren EMG-Aktivität vor und nach Mandibularanästhesie festgestellt wurde, und aus Patienten mit Trigeminusneuralgie, deren EMGs vor und nach Blockade des Ganglion Gasseri aufgenommen wurden. Zwischen dem Sprechen ohne Anästhesie und dem bei einseitiger oder beidseitiger Anästhesie war keine hörbare Veränderung zu vermerken. Als besonderes Charakteristikum war im allgemeinen eine Zunahme der Aktivität vor dem Sprecheinsatz und der Untergrundaktivität und vor allem der Artikulationsaktivität festzustellen. Diese Zunahme zeigte sich symmetrisch auf beiden Seiten, auch bei einseitiger Anästhesie, und war im wesentlichen auf die Muskeln beschränkt, die in der Produktion der betreffenden Sprachlaute am zweckentsprechendsten sind, während die Co-Kontraktionsaktivität der antagonistischen Muskeln abnahm. Diese Aktivitätszunahme war zudem oft mit einem früheren Einsetzen der Artikulationsaktivität verbunden. Die Kontextabhängigkeit der EMG-Aktivität war bei der Erzeugung von Vokalen deutlich verschlechtert, dagegen nicht bei der von Konsonanten. Die angeführten Befunde in den EMGs werden im weiteren im Zusammenhang mit Veröffentlichungen anderer Autoren über die Auswirkungen der De-Afferentierung der Gliedmassen und der interkostalen Muskulatur diskutiert. Wie daraus zu entnehmen ist, lassen sich die Änderungen im EMG die nach Blockierung der afferenten Aktivität des Trigeminus festzustellen sind, nicht durch eine Störung eines peripheren Rückkopplungskreises, ähnlich wie er beim Gamma-System vorliegt, erklären, und ein solcher Rückkopplungsmechanismus scheint daher für die Sprachproduktion der Erwachsenen nicht notwendig zu sein. Die Befunde könnten sich jedoch durch eine Störung der Positionswahrnehmung erklären lassen. Um die Störung zu kompensieren, konnte etwa die Kontrolle der Artikulationsaktivität, die normalerweise unbewusst vor sich geht, von einem höheren Niveau des Zentralnervensystems übernommen werden, und eine solche bewusstere Kontrolle der Motorik könnte die erhöhte Muskelaktivität und den Mangel an Kontextabhängigkeit der EMG-Aktivität erklären.

ACKNOWLEDGMENT

The authors gratefully acknowledge the co-operation of oral surgeons from the Department of Oral and Jaw Surgery and B. A. Meyerson, M.D Department of Neurosurgery

ject who was anaesthetized on several occasions. Bilateral mandibular anaesthesia has been used before in speech research by Mc Croskey (1958) and Ringel & Steer (1963) whose listener tests revealed significant articulatory inaccuracy under the influence of anaesthesia. The absence of any audible changes in the articulation in the present study may reflect differences between the phonetic test materials Like Ringel & Steer (1963), we found that the speech remained highly intelligible with anaesthesia.

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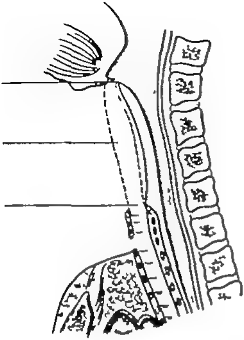

1 Semi-schematized illustration of the operation dure: larynx removed, pharynx fistula (*Ph*) and tracheostoma (*o T*) connected by a newly d dermic tube (*H.R.*).

of the sick persons treated continued essional careers, 4 of them could be fully ·orporated into working life after re ing 11 patients were already pensioned, o longer working, at the date of opera-

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ADVANTAGES AND FAILURES OF THE METHOD

essential disadvantages of the method are:) the fact that the patients make a poor ain by having constantly to wear a can- instead of being able to speak without from the first insertion of a speech-can-

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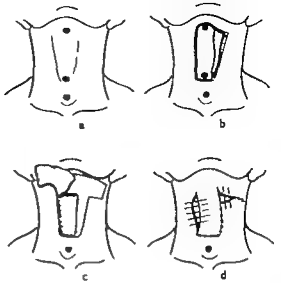


Fig 2 (*a–d*) Preparation of the inner and outer flap for the establishment of the praepharyngeal air tract.

treatment for the basic disease (laryngectomy) and the postoperative irradiation usually necessary after localization of the tumour

Asai (1966) Miller (1967 1971) McGrail (1970) and recently v Schulthess (1971) mention the dangers and problems of asperation of saliva and food particles via the newly formed mucodermal connection between pharynx and

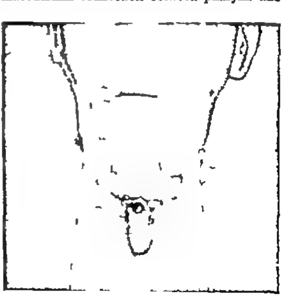
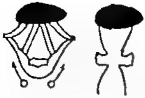


Fig 3 Final state after modified Asai-operation. (277)

Table I. *Five years experience with plastic voice rehabilitation after laryngectomy (modified Asal technique) from 1967 to 1971*

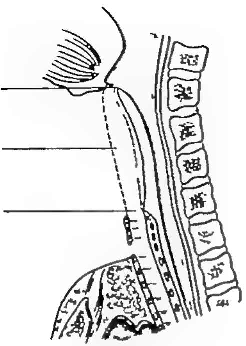
		>1 year	>2 years	>3 years	>4 years	>5 years	Vocal function
	7 whereof 7 without symptoms	—	—	2	2	3	5 good, 2 inadequate
	6, whereof 5 without symptoms	—	2	2	—	1	2 good, 1 adequate 1 inadequate
	6, whereof 5 without symptoms	2	2	1	—	—	4 good, 2 inadequate
	5, whereof 3 without symptoms	1	1	1	—	—	2 good, 1 adequate
	Total, 24 cases, whereof 20 without symptoms	3	5	6	2	4	

lacement voice from the oesophagus has been well or satisfactorily established (this being in my opinion still the best solution for a voice restoration), I refrain from plastic vocal rehabilitation. In other cases however I carry out the operation in the aforementioned modification within one session after postoperative irradiation (usually necessary because of the tumour localization) was finished.

Again, I must emphasize that only critical selection and a firm indication can prevent us from transforming a possibility which has proved successful in certain cases, into a rule which then might well contradict the principles of carcinoma treatment.

RESULTS

Table I sets out the tumour dimensions in the 24 cases where a modified Asal-graft for voice rehabilitation after laryngectomy was carried out. The subdivision into four groups made according to the supraglottic tumourous dimensions, shows that the tumourous localization presupposing the initially mentioned indication for operation, has less influence on the vocal function desired, but more on the general course of the disease. Here the interval between operative removal of the tumour and the postoperative irradiation necessary in nearly all cases is of special concern—an interval which usually is rather lengthy. The vocal function acquired was good in 16 cases, adequate in 3 cases and inadequate in 5 cases.



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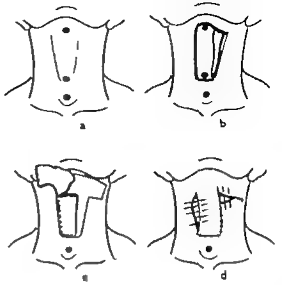

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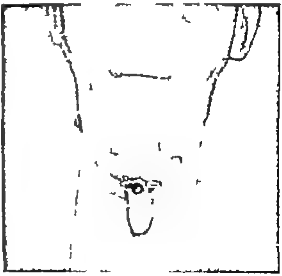

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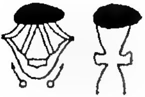	7 whereof 7 without symptoms	—	—	2	2	3	5 good, 2 inadequate
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TRACHEOSTOMY IN SUBGLOTTIC LARYNGITIS (PSEUDOCROUP) AND ACUTE EPIGLOTTITIS

J Tarkkanen and A. Kohonen

From the Otolaryngological Hospital University of Helsinki Helsinki, Finland

(Received November 1 1971)

ract Of a total of 525 patients with subglottic gitis (pseudocroup), 10 (2%) were treated by eostomy In cases of acute epiglottitis, the pro- on of tracheostomies was far higher 11 out of ses, or 48% On admission the majority of the nts were in an extremely low condition and suf ion threatened. Thus 11 were subjected to eostomy immediately There was no post ative mortality Difficulties in decannulation oc- d in the youngest patient, an infant, aged 3 / hs. In severe cases of pseudocroup and epi- tis, tracheostomy is still of importance as it opens he airways. The use of prolonged nasotracheal ation and tracheostomy is compared on the basis is study

recent years tracheostomy has been in- singly supplanted by prolonged naso- heal intubation in the treatment of res- ory difficulties of infants and children. rative complications of tracheostomy such ediastinal emphysema, pneumothorax and orrhages, can be avoided by using intuba treatment (Abbott, 1968) In the case of ren, however, sufficient attention has not ys been directed to the basic disease h is the cause of tracheostomy nor has effect of the child's age on the final out n always been closely studied. Oliver et al. 2) analysed in detail 294 cases of tra- stomy performed on children. The sub- were under 13 years, 40% under 2 years ge. Operative mortality occurred in 6.5% re were postoperative complications in 55 ents, or 19% Of the 40 children in whom utaneous emphysema, mediastinal em- ema or pneumothorax developed after ation, 31 had laryngotracheobronchitis, epiglottitis or diphtheria. The mortality as- sociated with the tracheostomy itself was 3 4% Five patients died as a result of the operation itself or because it was not per formed early enough, 5 died during the post operative period, and 3 because the cannula slipped out or plugged up Overall mortality was 20.1% It arouses attention that the highest mortality (54.3%) occurred in the cases tracheostomized for central nervous dis- orders, whereas those operated because of laryngeal infection had the lowest mortality in the series, 5.3%

Those laryngeal infections in which, be cause of respiratory difficulties, tracheostomy must now and again be resorted to, are sub- glottic laryngitis (pseudocroup) and acute epi- glottitis. The former is often associated with tracheitis and is usually attributed to virus infection, especially parainfluenza virus, though Echo and Coxackie virus have also been found (Vivell, 1970). Among bacteria, *Haemophilus influenzae* and streptococci pre dominate. Epiglottitis is most often due to *Haemophilus influenzae* (Sinclair 1941 Beren- berg & Kevy 1958).

The incidence of tracheostomy among hospitalized patients with subglottic laryngitis is markedly lower than in the case of epi- glottitis. In the former Estola et al. (1960) reported an incidence of 48/794, or 6% In Beckmann's (1970) studies it varied from 5% to 15% whereas in epiglottitis it was between 50% and 85% Vainer & Ludvigsen's (1962)

material consisted of 17 children with epiglottitis, 11 of whom were tracheostomized. Rosales & Davenport (1962) reported on 51 children 90% of whom underwent tracheostomy In Träff & Bak-Pedersen s series (1968) 9 out of the total of 12 patients were subjected to tracheostomy A very low incidence of tracheostomy was reported by Kyttä (1960) in his series this operation was re sorted to in only 1 of 17 epiglottitis patients.

A total of 525 patients with subglottic laryngitis (pseudocroup) and 23 with acute epiglottitis were treated during the period 1965–1968 in the Otolaryngological Hospital, University of Helsinki. During each of the 4 years under review the patients with the former disease numbered 104 109 175 and 137 respectively and for epiglottitis the cor responding figures were 3 6 5 and 9 The youngest patient in the whole series was $3^1/_2$ months, and the oldest 88 years of age. Aver age age was 4 years 7 months. The tracheostomies performed are dealt with in greater detail below

TRACHEOSTOMIZED CASES

Tracheostomy was performed on 10 of the 525 patients with subglottic laryngitis (2%). In epiglottitis, however the corresponding gures were 11 of 23 (48%). Thus tracheoomy was made in 21 cases altogether

Of the patients treated by tracheostomy 19 were children and 2 adults. The youngest child was $3^1/_2$ months, the oldest 8 years of age. The age distribution was similar in subglottic laryngitis and in epiglottitis. The largest group consisted of the 1–2 year-olds: it included 4 children with each of the two diseases studied. The 2 adults tracheostomized because of epiglottitis were 39 and 56 years of age

On admission, 2 patients were in satisfactory condition while the condition of 6 was distinctly affected, moderately severe In addition to dyspnea there was restlessness, cyanosis and fatigue. The largest group consisted of 13 patients who when admitted, were in poor condition at the last stage of laryngeal dyspnea (stadium suffocationis). Cyanosis had disappeared and the skin was pale. The patients were limp and on the point of suffocation. No difference in status at admission emerged when the two diseases were compared. Among 4 patients admitted in a state of superficial unconsciousness there were two suffering from each disease. Except in 2 cases of subglottic laryngitis, the disease had developed within 24 hours. Fever (38–40) on admission was recorded in 19 patients, only 2 patients with pseudocroup were free from fever

Tracheostomy was performed immediately on 11 patients, 7 suffering from epiglottitis and 4 from pseudocroup. Eight patients were tracheostomized within a few hours of admission and 2 after more than 24 hours.

The trachea was exposed above the thyroid gland, through a transverse incision. It was opened at the level of the 2nd–3rd tracheal rings. In 10 cases a window was prepared by removing cartilage from the anterior tracheal wall, in 10 others a flap hinged below was formed from the anterior wall and sutured to the subcutis; in one case a vertical incision was made in the anterior wall. The cannula inserted into the trachea was of metal.

Operative complications occurred in a 2-year-old child with pseudocroup. After operation there was irregularity of cardiac function, and the child was referred to the Children's Hospital University of Helsinki.

Postoperatively a 1 year-old child with pseudocroup was found to have pneumothorax in the upper part of both chest cavities; according to the pediatric surgeon the pneumothorax was not due to the surgical intervention but resulted from the child's struggle to get enough air before operation. A child of 4 years with epiglottitis was found, on the 10th postoperative day to have purulent meningitis due to *Hemophilus influenzae* that had caused prolonged high fever *Hemophilus influenzae* was cultured from the cerebrospinal fluid but not from the laryngeal sample.

In addition to the above 3 children, a $3^1/_2$ months old child with pseudocroup had to

sferred to the intensive-care unit of the dren s Hospital because of failure of *decanulation*. The 17 others were subjected to nnulation 5 to 26 days following traostomy the average interval being 7 days.

CASE REPORT

infant born on June 23 1967 developed rseness and cough over a week before adion to hospital (Oct. 3 1967). When added he had dyspnea and inspiratory stridor re was no fever A superior tracheostomy performed during the same day and a ow made in the anterior tracheal wall at level of the 2nd–3rd tracheal rings. The ent was decannulated for the first time on 9 and did fairly well until so great dif ties in breathing appeared that the wound to be opened under anesthesia and the nula reinserted on Oct. 13 The patient decannulated on Oct. 19 but inspiratory or increased so much the next day that cannula was introduced for the third time. recovery from anesthesia the baby was and respiration superficial. He was there transferred to the intensive-care unit of Children s Hospital, where decannulation performed on Oct. 28. The baby was harged from the hospital on Nov 3 1967 1 month after admission to hospital. yngeal dyspnea recurred on Nov 13 nasoheal intubation was carried out and the ent sent home on Dec. 8. The following 1968 the patient was admitted to the ldren s Hospital three times for acute iratory difficulties, but neither intubation tracheostomy proved necessary During 9 the child was in the hospital because of iratory tract infection but no special sures were needed on this occasion either yngotracheoscopy was made when the d was 2 years of age and showed slight ging of the left lateral wall of the subtis towards the lumen, but no actual ste is was diagnosed. The patient has not ded hospital treatment since then.

In *follow-up examination* in 1969–1970, 11 of the 21 tracheostomized patients were seen 6 of them had had epiglottitis and 5 pseudocroup. In none of those examined had the same disease recurred. All were subjectively free from symptoms. The laryngeal status was normal, and so were the laryngeal and tracheal X-rays, apart from a slight flat collapse of the anterior wall at the site of tracheostomy Tracheoscopy was not performed because the patients were all symptom-free. None of those 10 who did not come for follow-up, has later been treated for respiratory disorders according to hospital records they are all symptom-free.

DISCUSSION

A number of fairly severe cases of acute respiratory insufficiency due to subglottic laryngitis or acute epiglottitis have been dealt with above. All the patients were treated by superior tracheostomy and 13 out of the total of 21 were emergency cases. None of the patients died and in none did any complications cause permanent trouble.

The aim of therapy in severe respiratory disorders is to preclude mechanical occlusion of the larynx and trachea, treating at the same time the associated hypoxia. It depends entirely on the existing circumstances whether intubation or tracheostomy should be used for opening the airways. Treatment with intubation can only be done in the intensive-care unit, and since these are not available in all hospitals, tracheostomy is still usually the life-saving procedure. It should be noted, in addition, that the tube passed through swollen epiglottis or subglottis is much smaller in diameter than is the tracheal cannula. Tracheostomy results in diminution of the dead space in the airways and contributes to ease respiration. The energy expended in breathing is also reduced. Bosina & Wurnig (1968) found that, as a result of tracheostomy the ratio between the effective respiratory minute volume and the dead space changes from 1 1 to 2.1

Naturally there are reports on successful intubation treatment of severe cases of pseudo-

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X RAY EXAMINATION AND SINOSCOPY IN MAXILLARY SINUS DISEASE

P Illum, F Jeppesen and E. Langebæk

From the Departments of Otolaryngology and X-ray Diagnosis University Hospital Odense Denmark

(Received February 12, 1972)

ract A comparison between the results obtained
y X-ray examination and endoscopy (sinoscopy)
he maxillary sinus has not previously been pub-
d. In the present series 585 maxillary sinuses
examined by both methods. In 3% of the cases
ere unable to accomplish sinoscopy and in 9%
ay have overlooked the changes seen on the
y pictures. Sinoscopy was superior to the X-ray
ination in the remaining cases, giving more exact
rmation for differential diagnosis of the type and
e of the changes found in the sinus. An exact
osis by X-ray was not obtained in 29% of the
scopical diagnoses, although this could reason-
have been expected. The presence of discharge
incorrectly diagnosed at X-ray examination in
of the cases. Sinoscopy can give valuable in-
ation in cases of malignancy of extension to the
llary sinus prior to irradiation or surgery. Con-
ently in many cases one must consider whether
standard X-ray examination of the sinus can be
aced by sinoscopy

value of X-ray examination of the para-
al sinuses in cases of maxillary sinusitis has
n the subject of relatively few investiga-
s. The criterium referred to in all publica-
s is the presence of discharge in the sinus
nd at puncture and irrigation. This litera-
was reviewed by Axelsson et al. (1970).
se authors used four standard projections:
ipito-mental, occipito-frontal, lateral and
axial projections with the patient in the
position and horizontal direction of the
tral beam. Only in 24% of the cases with
retion could this be demonstrated on the
ay pictures. However by including a 5th
jection, the occipito-mental with the patient
recumbent position and the affected side downwards, the reliability of the X-ray examination increased to 88%

It is necessary however to bear in mind that a large number of healthy persons have X-ray abnormalities of the maxillary sinus. Fascenelli (1969) subjected some 400 young persons, who were healthy or had minor diseases having no relation to the nose to X ray examination, and found abnormalities in 26% of the cases. A cyst or polyp was found in 9% 5% showed marked thickening of the mucosal lining, and 12% had slight or moderate thickening of the mucosa. These findings were not considered as requiring any treatment, and it is doubtful if they should be regarded as indicating a disease in all cases.

Endoscopy of the maxillary sinus (sinoscopy) often gives good information on the condition of the antral mucosa (Bauer & Wodak, 1959 Timm, 1965)

However no comparison between the results of sinoscopy and X-ray examination has been carried out previously

METHOD

In the period November 1969 to February 1971 sinoscopy and X ray examination was carried out whenever sinus disease was suspected. The technique used and typical findings have been published earlier (Illum & Jeppesen, 1972) About two-thirds of the examinations were performed under local anaes-

Table I *585 maxillary sinuses examined by X-ray and by means of sinoscopy*

	Sinoscopy failure due to				Sinoscopy incomplete due to			
	Patient too disagreeable	Pronounced septum deviation	Osseous wall too hard	Perforation to para-pharyngeal fossa	Tissue touches the lens	Bleeding spoils view	Discharge spoils view	Sinoscopy complete
No. of maxillary sinuses	3	2	14	1	19	29	7	510
Total		20				55		510
Percentage of whole material		3.4 % (2.1–5.2, $p=0.05$)				9.4 % (7.3–11.9 $p=0.05$)		[illegible] ([illegible], $p=0.05$)

thesia, the remainder under general anaesthesia, partly because of other operative procedures performed simultaneously (e.g. adenoidectomy bronchoscopy). The youngest patients were 6 years of age.

The sinoscopic appearance of the mucosa was classified into the following groups: *1* Normal. *2* Localized or generalized oedema with or without acute inflammation or secretion. *3* Polypoid or fibrotic changes with or without secretion. *4* Cysts *5* Solitary polyps. *6* Malignant tumours. *7* Benign, nonpolypoid tumours. All the diagnoses were based upon the macroscopical appearance of the mucosa

The X ray examination was performed with he patient in a recumbent position and a verti- central beam using four standard projections. the occipito-mental (Pine) the occipito-frontal (Stenhuis) the lateral and the full axial (Welin) If secretion was suspected from these, a 5th projection was added. the occipito-mental with the patient sitting, and horizontal central beam.

The valuation of the pictures was carried out retrospectively by the authors without using the information obtained from the case histories or the sinoscopy The following classification was used. *1* Normal. *2* Thickening of mucosal lining <2 mm (slight thickening). *3* Thickening of mucosal lining 2 mm but less than half of the diameter of the sinus (moderate thickening) *4* Thickening of the mucosal lining greater than half of the diameter of the sinus (subtotal thickening). *5* Total opacity *6*. Solitary cyst/polyp. *7* Cyst/polyp in combination with thickening of the mucosal lining. *8* Level of secretion. *9* Tumour with without destruction.

MATERIAL AND RESULTS

The whole material of 585 sinuses is shown in Table I In 20 cases (3.4% of the whole material) we were unable to accomplish the sinoscopy The reasons for this are seen from the table.

In 55 cases (9.4%) no clear picture of the mucosa was obtained However secretion, when present, could be diagnosed and a biopsy from the mucosa could be taken, so that the examination gave essential information on the condition of the mucosa.

Both successful sinoscopy and X-ray examination was carried out in 510 sinuses, and these are listed in Table II. In many cases more than one sinoscopical diagnosis was made in the same sinus (e.g. acute sinusitis + mucosal cyst) As could be expected, a number of sinoscopical diagnoses were found to correspond to each X ray diagnosis

The appearance of discharge is shown in Table III In 212 out of 232 cases (91.4%) with secretion found at sinoscopy this had not been visualized by X ray while in *11* cases out of 353 (3.1%) without discharge at sinoscopy secretion had been demonstrated on the

le II. *Diagnoses in 510 maxillary sinuses examined radiologically and by means of complete sino-y*

	Sinoscopical diagnoses						
	Normal	Localized or generalized oedema or acute infection	Polypoid and fibrotic changes	Cysts	Polypoid tumours	Malignant tumours	Non polypoid benign tumours
y diagnoses							
mal	33	14	6	3	—	—	—
t thickening of cosal lining	9	4	—	—	—	1	—
erate thickening of cosal lining	50†	90	96	10*	8	—	—
otal thickening of cosal lining	5	58	48	9	2	1	—
l opacity	4	32	14	5	—	—	—
p or cyst	2†+4	10*	6	35	8	—	—
p or cyst and cosal thickening	4	6	11	7	—	—	—
our with truction	—	2	—	—	—	2	1
our without truction	1	1	—	—	—	—	—
l	112	217	181	69	18	4	1

dicates that the X-ray examination has given incorrect or insufficient information.
re used for diagnoses where the changes visible on the X-ray pictures are or might have been overlooked ng sinoscopy

ay pictures. On the whole X-ray was mis-ing with regard to the presence of secre ı in 223 of 585 cases (38 1 %)

The malignant diseases and benign non-ypoid tumours examined are listed sepa ly because of the special interest of this ticular group (Table IV). The histologic e and the primary localization is shown for h of the cases. There was a more or less nounced blurring of the sinus in all cases normally found total opacity Radiological evidence of tumour dissemination within the sinus and the presence of a tumour during sinoscopy and biopsy is shown in the table. It can be seen that most of the cases are malig nant tumours in the adjacent regions, and the diagnosis was mostly obtained by means of a biopsy from a more easily accessible cavity than the sinus.

In case 1 sinoscopy gave rise to suspicion of malignancy although neither the biopsy nor the material obtained from the subsequent

le III. *Demonstration of discharge in the maxillary sinus by X-ray examination and sinoscopy ressed as numbers of sinuses*

	Discharge demonstrated by sinoscopy	No discharge by sinoscopy	Total	X-ray diagnosis incorrect
charge demonstrated X-ray examination	20	11	31	223 38,1
charge not visible X-ray examination	212	342	554	(34...–42.2 ...)
al	232	353	585	(p = 0.05)

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Percentage of whole material		3.4 % (2.1–5.2, $p=0.05$)				9.4 % (7.1–11.9, p 0.05)		87 (84.4–[illegible], p [illegible])

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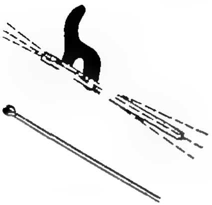
The appearance of discharge is shown in Table III. In 212 out of 232 cases (91.4%) with secretion found at sinoscopy this had not been visualized by X-ray while in 11 cases out of 353 (3.1%) without discharge at sinoscopy secretion had been demonstrated on the



1 The trocar is introduced into the antrum. The limited area from which biopsy can be taken, is ...trated.

...ked with * in Table II. This applies to ... and solitary polyps, for instance, which ... not visible on the X-ray and to 17 ... where sinoscopy revealed normal con... although total or subtotal opacity or ... were seen on the X-ray pictures. Informa... required for the differential diagnosis ... be expected from cases where the films ... complete or subtotal opacity apart from ... cases where the sinoscopical appearance ... normal.

... is worth noting that in 56 sinuses with ... X-ray pictures, pathological conditions ... found in 23 cases (41%) Most often we ... localized oedema on the floor of the ... or fibrotic changes, but 3 cases of small ... were overlooked at the X-ray examina... Therefore, had the material been large ...ugh, this group might have included an ...y case of malignancy

... have found normal conditions during ...scopy in 112 sinuses. In 42 of these (38%) ... agreed with the X-ray examination, which ...aled a normal sinus or slight thickening ... the mucosa. In 17 cases (15%) the X-ray ...ination showed pronounced abnormalities ... sinus, total or subtotal opacity or cysts, in spite of the normal condition stated at sinoscopy

Table V *Comparison of reliability of sinoscopy and X ray examination of the maxillary sinus (cases with tumours omitted)*

	No. of sinoscopy diagnoses	Per cent of total	Confidence limits $p = 0.05$
Sinoscopy diagnosis in agreement with X-ray diagnosis	371	62.5	58.5–66.4
X-ray diagnosis incorrect or inadequate	170	28.7	25.1–32.5
Sinoscopy diagnosis possibly or certainly inadequate	52	8.8	6.7–11.4
Total	593		

However in 52 cases (46%) or 8.8% of the total material we suspect that the changes demonstrated by X ray were or might have been overlooked during sinoscopy (in Table II marked with †) The X ray examination revealed moderate thickening of the mucosa in 50 sinuses, and in 2 cases with polypoid swelling of the medial wall of the sinus this was not visible at sinoscopy although it was confirmed by tomography (Table V) Some of these cases might possibly be explained by the fact that the metaoxedrine solution always used in the middle meatus in order to diminish the bleeding caused by the puncture, may have caused some of the oedema in the maxillary mucosa to disappear too.

In nearly 63% of the diagnoses there was agreement between the two diagnostic procedures (Table V) However in many cases sinoscopy gave valuable information regarding the differential diagnosis, which was not obtainable from the X-ray pictures e.g. the cases with total or subtotal opacity of the sinus.

Our investigation with regard to the presence of secretion reveals an extremely low degree of confidence of the X ray examination in comparison with other investigations (Axelsson et al., 1970) With particular reference to this, it should be noted that X ray examination at this

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INCIDENCE OF BACTERIA, L FORM AND MYCOPLASMA IN CHRONIC SINUSITIS

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ract. A series of 50 cases of chronic sinusitis (82 ses) has been studied to establish the relative roles h bacteria, L-form and mycoplasma play in the ation of chronic sinusitis. L forms were found to he commonest organism, identified in 20.7% of inuses, whereas the dominant bacteria was *Beta* Streptococci isolated in 12.22%. Of 52 bac logically sterile sinuses, L-forms were isolated in hich reveals their pathogenic nature. The impor role of L form in maintaining the chronicity of infection must be watched, as this transitional L may revert to the infective bacterial form under vourable physical conditions or the organisms selves may be pathogenic. Mycoplasma was not d in any of these cases.

re are significant variations in the bac ological findings reported in the different es. Such variations may be ascribed to fac such as different sampling techniques stad et al., 1964) and seasonal variations an et al. 1967) Björkwall (1950) and pon & Vogelsang (1956) pointed to the ible risk of staphylococcal contamination he antral irrigation fluid evacuated through nose. Palva et al. (1962) considered the ence of a small number of staphylococci to an index of a correct sampling technique. in, bacteriological studies of many chronic sitis cases prove sterile (Sparrevohn & h, 1946 Urdal & Berdal 1949 Björkwall, 0 Paquet et al., 1956 Palva et al., 1962 tad et al., 1964 Kinnman et al 1967) in rwise proven cases of sinus infection.

uring recent years there has grown an increasing awareness of the role of L-forms causing diseases. *L-forms* are bacterial variants, bacteria which have lost the cell wall. They are produced under several circumstances, such as in presence of antibiotics which interfere with cell wall synthesis, lysozyme, phage, antibodies, complement, etc. The existence of the *infectious agent in transitional or L form may* be an important factor in causing the chronicity of the disease process, L-forms affording prolonged persistence of the causative bacterial agent and their reversion to the parent bacterial form causing relapse after apparent control under favourable conditions such as decreased body resistance. Nevertheless, L forms themselves may be pathogenic, since they liberate toxins similar to those of the parent bacteria (Sharp et al., 1957 Mattman et al., 1961 Karakawa et al., 1965) and have been isolated from several diseases without any associated bacteria.

The pathogenic role of mycoplasma in human respiratory diseases has been established recently following their demonstration as being the etiological agent in primary atypical pneumonia. They have been isolated as causative organisms in naturally and experimentally produced pharyngitis (Chanock et al., 1961 Couch et al. 1964 Mufson et al., 1965) and otitis media cases (Chanock et al. 1961 Rifkind et al. 1962, Soběslavský et al., 1965).

Table I. Showing the details of the bacteriological findings

Organisms	Uni-lateral	Bi-lateral	Total of sinuses	Per centage (approx.)
Beta hemolytic streptococcus	6	2	10	12.22
Staphylococcus pyogenes	4	1	6	7.31
Hemophilus influenzae	5		5	6.1
Klebsiella aerogenes	3		3	3.65
Diplococcus pneumoniae	2		2	2.44
Anaerobic strepto-coccus, Group VI–A		1	2	2.44
Mima polymorpha	2		2	2.43
Total			*30*	*36.6*
Sterile cases	14	19	52	63.4
Total			*82*	*100*

L-forms were, however isolated most frequently These were detected in 17 out of the total 82 sinuses as shown in Table *II*

MATERIAL AND METHODS

Fifty cases of chronic maxillary sinusitis of more than 6 months duration were studied Only those patients were included in this series who had not undergone any form of antibiotic treatment within the previous 3 months. Another 10 normal cases were studied for comparative analysis. *After taking the history and* routine ENT check-up the infectious state in the maxillary sinuses was finally assessed from radiological *examination by 45° occipito-men*tal view and antral irrigation. The findings were graded as advocated by McNeil (1963) Antrum puncture was carried out under strict asepsis Gentle aspiration was carried out for collection of sample with a 20 ml syringe fitted to the cannula with an adaptor *If no fluid* could be aspirated the patient's head was kept bent so that the punctured sinus remained undermost to prevent the entry of saline water into the nasal cavity Saline water was instead injected slowly into the sinus in 10 ml quantity and aspirated rapidly

The specimens were taken immediately to the laboratory Following preliminary smear examination these were inoculated into routine bacteriological media and incubated both aerobically and anaerobically at 37°C. Further isolation and identification of bacteria were done *in the usual manner Part of* the collected sample was filtered off by the sinter glass filter G 3/5 to render it bacteria free. Part of the filtrate was inoculated into modified Edwards media, both broth and agar containing antibiotics *(Agarwal & Ganguly 1969) for* culture of L form. After 1 week these were examined under phase contrast high power microscope for the characteristic colonial morphology The remainder of the filtrate was used for culture of mycoplasma in PPLO broth and agar (Hayflick et al 1962) After three weekly passages in PPLO broth, incubated at 37 C both aerobically and anaerobically reinoculation into PPLO agar plates was done. After 3 days incubation at 37 C, these were examined under light microscope for the presence of mycoplasma colonies.

Ten normal antral samples were collected from patients undergoing surgery under general anaesthesia. The possibility of sinus infection was excluded by the absence of suggestive signs and symptoms, the normal X-ray findings and clear aspirations obtained from the sinuses.

RESULTS

Eighty-two sinuses were found to be infected in 50 chronic maxillary sinusitis cases. The average duration of illness was 5 years The disease was found to be prevalent in the third and fourth decade of life with males affected twice as frequently as females. The disease was bilateral in 32 cases and unilateral in the rest. *The diagnostic value of radiology* was found to be much greater than the transillumination test, as shown by the final proof of antral lavage Transillumination test was positive in only 63% of cases whereas radiological evidence of infection was found to be correct in all of them. No strict *relation* was found to

:t between the severity of the radiological ling and that of antral wash, although the nges of the turbidity and purulent character ntral wash-out signifying worse pathological nges increases with the severity of the radiocal findings. Of the 82 sinuses studied, 52 ses were found bacteriologically sterile. In remaining 30 sinuses, *Beta hem.* streptoci were the dominant bacteria. *Staphylocus pyogenes* and *Hemophilus influenzae* less significant roles. Details of the bacological findings are shown in Table I.

arge gram-negative bodies measuring 7 μm liameter were seen most frequently. On subure in ordinary media these did not revert acterial form except in one instance where *nophilus influenzae* L-form, and bacterial n were found together. Incidence of L-forms frequent in the younger age group. L-forms e present in the more long-lived chronic sitis cases. Almost two-thirds of the cases ibiting L-forms had the illness for more 3 years.

Iycoplasma could not be detected in any hese cases. Normal sinuses were found to ssentially sterile.

DISCUSSION

method of collection of sample by direct ration technique enabled us to avoid nasal tamination. This also prevented the me ical dispersion of the fluid which had the of destruction of mycoplasma and L-forms. ulation immediately after collection pre ed destruction of organisms particularly *Diplococcus pneumoniae* and *Hemophilus enzae* (Lystad et al., 1964). In contrast apinskie & Flakes (1967) Dienes (1967) Dienes & Bullivant (1968) we used lified Edwards media with 500 units of cillin/ml. This amount of antibiotic proved suitable for isolation than the induction -forms.

lifty-two sinuses were bacteriologically ile forming the largest group, of which 12 ses yielded L-forms showing that these were not truly sterile. The importance of L-forms lies in the fact that they have been repeatedly isolated from many of the disease processes, in which after energetic treatment with antibiotics, the causative bacteria are transformed into L-forms and these again produce the disease by reversion to the parent bacterial form (Lapinskie & Flakes, 1967). Guze (1966) demonstrated their formation experimentally following inadequate antibiotic treatment. As the general population today takes antibiotics erratically and especially of the penicillin group induction of L-form is not an improbability. L-forms in sinuses may have been produced by the presence of lysozyme and local antibodies in the nasal tract. The vicinity of the paranasal sinuses to the stronghold of bacteria in the nasal cavity and their relatively closed atmosphere makes these easily vulnerable to either the L-forms primarily or to bacteria, which later become converted to L-forms.

Table II. *Incidence of L-forms*

L-form present	No. of sinuses	Percentage (approx.)
Sterile cases	12	14.6
With other bacteria	5	6.1
Total	17	20.7

ZUSAMMENFASSUNG

Eine Reihe von 50 Fällen der chronischen Sinusitis (82 Sinusen) ist untersucht worden, um die relative Rolle der Bakterium L Form beim Verursachen der chronischen Sinusitis zu zeigen. Die L-Formen sind als die einfachsten organismen in 20,7 Prozent aller Sinusen identifiziert worden, weil das herrschende Bakterium Beta Hem. in 1..22 Prozent der Fälle isoliert war. Unter den 5 bakteriumsterilen Sinusen wurden L-Formen in 12 Fällen isoliert, das zeigt ihre pathogenische Beschaffenheit. Die wichtige Rolle der L-form beim Erhalten der Chronizitat der Infektion muss beachtet werden, weil diese transitionalen L Formen unter ungünstigen physikalischen Bedingungen in infektive Bakterium-Form zurück verwandelt werden können oder die Organismen selbst pathogenisch sein können. Mycoplasma wurde in keiner von diesen Fällen gefunden.

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SCLEROSING INFLAMMATION OF THE SUBMANDIBULAR SALIVARY GLAND (Küttner Tumour)

A Progressive Plasmacellular Ductitis

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(Received January 5 1972)

ract. Eleven cases of sclerosing inflammation of submandibular salivary gland or Küttner tumour seen during the period 1965–1971 Only about ses have been reported in any detail previously ably it is much more common than has been as- d and it deserves special interest because these are usually diagnosed as neoplasms. The etio- is discussed. The abundant accumulations of hocytes and plasma cells and the perivascular ses resembling fibrinoid degeneration noted in topathological examinations are tentatively at- ted to autoimmunization.

er in 1896 was the first to describe the cal and histopathological concept of ne unspecific inflammation of the sub- dibular salivary gland and he reported cases of his own. This condition has later referred to as Küttner tumour" or as nic sclerosing sialoadenitis of the sub- mandibular gland. It is well known and has been discussed especially in the German litera- ture (Küttner 1896 Steinhaus, 1905 Thaysen, 1910 Ganner 1929 Rauch, 1959 Seifert, 1965 1966) but rarely in other languages (Papoulacos, 1949 Bagnoli, 1957 Zillotto 1967) The Küttner tumour is a specific entity and of particular interest because these cases are usually diagnosed clinically as neoplasm.

e I. *Age and sex classification of Küttner nts and duration of illness*

Sex	Age (years)	Duration of illness
♀	18	5 years
♂	49	2 years
♂	43	2 months
♂	31	2 months
♂	53	6 months
♂	53	4 months
♂	48	3 years
♀	31	2 months
♂	55	1 month
♀	72	3 years
♀	46	1 year

MATERIAL AND CLINICAL APPEARANCE

Eleven cases of Küttner tumour of the sub- mandibular gland were diagnosed during the years 1965–1971 in the Departments of Oto- laryngology and Pathology in Oulu Univer sity Mean age of the patients was 45 years and the duration of illness averaged 1.5 years. There were 7 men and 4 women (Table I) In all cases the lesion was unilateral. In some of the cases, growth was periodic. The definitive size of the tumour was variable but usually did not exceed that of a hen s egg. The gland was firm on palpation and normal-looking secre tion was obtained on pressure. Clinically the picture resembled mainly a neoplasm, since there were usually no signs of infection. In our series, only one case showed sialectasia and salivary calculi The surface of the extirpated gland showed an increased and irregular lobu-

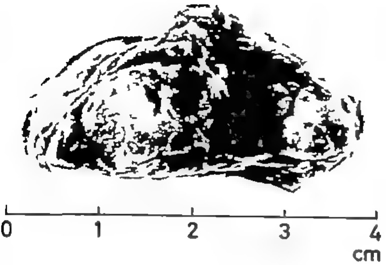


Fig 1 The gross pathology of the extirpated gland.

lation (Fig. 1). The outer surface was greyish and the cut surface, which was traversed by thick connective tissue septa, was greyish red.

HISTOPATHOLOGY

Selected specimens were fixed in formalin and embedded in paraffin. The 5 μ sections were stained with hematoxylin-eosin and meth green-pyronin stain. All lesions studied show a marked disturbance of the normal architec ture of the gland (Fig. 2). A characteristic feature was infiltration of lymphocytes and plasma cells in periductal areas (Figs. 3, 4). Even lymph follicles were found. The int

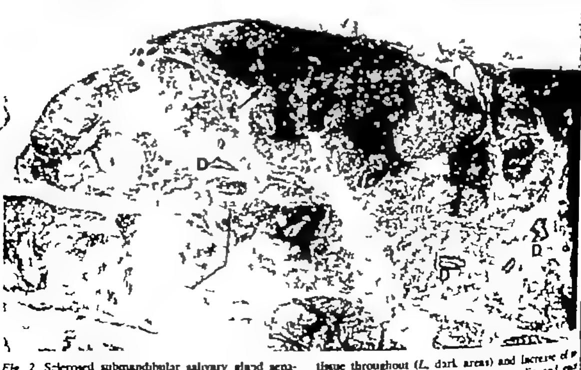
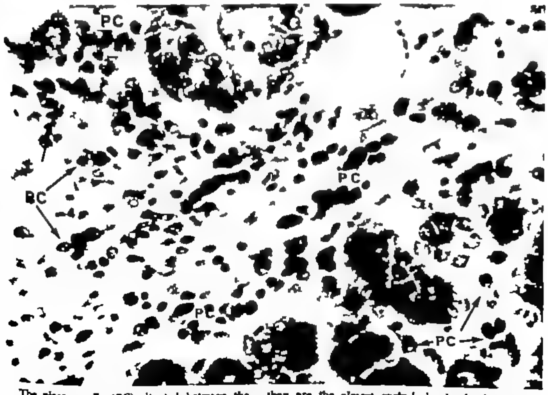


Fig 2 Sclerosed submandibular salivary gland separated into lobes by thick connective tissue septa. The interlobular ducts (*D*) are enlarged and degenerated. The gland parenchyma shows increase of lymphoid tissue throughout (*L*, dark areas) and increase of in teracinous connective tissue. Hematoxylin and eosin stain, × 9

The lymphoid tissue (L) with its lymph follicles (LF) is most abundant in periductal areas. In these areas the gland parenchyma has disappeared almost completely. Hematoxylin and eosin stain, 35



The plasma cells (*PC*) situated between the acini (*GA*) are further away from the ducts than are the almost exclusively dominating infl. m. Methyl-green-pyronin stain, 350.

Fig 5 Abundant increase and mucoid degeneration of interlobular connective tissue (C), enlarged inter lobular ducts containing mucoid-epithelial cell (D). Hematoxylin and eosin stain, 40

lobular ducts seemed to be affected first. Later e infiltration was found around the striated intercalated ducts In the advanced lesion the interlobular and intralobular ducts were embedded in thick fibrous trabeculae so that lobes of varying size were formed within the gland. Around some ducts, chiefly intralobular ones small deposits of fibrinoid material oc curred here and there in the lymphoid tissue Thick secretion and destroyed epithelial and inflammatory cells were frequently seen in the ducts. Secondary ductectasias were often found. In the areas of active fibroplasia basophilic mucoid material occurred in the connective tissue (Fig. 5) Finally there was glandular sclerosis and complete disappearance of gland acini, apparently as an end result of the scarring.

COMMENT

There has been disagreement on the etiolo and pathogenesis of chronic sclerosing infla mation of the submandibular gland. It has be attributed to congenital dilatation of the sa vary gland (Gerry & Selgman, 1955) or to i flammatory hyperplasia of the internal lymp oid tissue of this gland (Leonardelli & Ric 1956) Several authors have considered it d to some micro-organism, such as actinomyc (Ganner 1929), blastomyces or a coc (Kroiss, 1905 McKenna & Davis, 19 Städtler 1935) or to a virus combined w obstruction caused by salivary duct calcul (Bagnoli, 1957) According to Seifert's expe mental (1964) and clinical (1965) studies, t condition is caused by the length of the su mandibular duct system, its branching a

erticular formation, which offer favourable iditions for the accumulation of gland secre and to disturbances in the viscosity of mandibular secretions and in their elec yte content, especially calcium ion content. cording to this assumption an increase in latter leads to increased viscosity which y result in an obstacle to the flow of secre and formation of microcalculus and local t inflammation. All this may gradually se involvement of the whole gland by in mmation, with resulting fibrosis.

The abundant accumulation of lymphocytes plasma cells and the changes resembling oid material seem, in our opinion, to our an inflammatory process based mainly autoimmunization. It seemed to start in the er ducts and to progress towards the more al structures. The early plasmacellular in- on was followed by a progressive increase connective tissue leading first to periductal osis and later to scarring of the whole gland.

The following differential diagnostic pos- lities deserve attention: the syndromes of gren (collagen sialos) und Heerfordt (sar los) and tumours of the salivary gland. The mination can in most cases be made by phological or clinical methods. In Sjögren's drome, dacryosialoadenopathia atroficans, teral changes, joint pain and a high ESR ce in favour of this syndrome. The histo- ology of this lesion is known for instance a benign lymphoepithelial lesion (Foote & ll, 1954) or Sjögren-Syndrome with myo- thelial sialadenitis (Seifert 1966) It is dom- ted by diffuse lymphocytic infiltration of gland, while in the case of sclerosing sialo- nitis of Küttner an ascending progressive smacellular ductitis constitutes the essential on.

ZUSAMMENFASSUNG

Fälle von sklerosierender Inflammation der sub- dibularen Speicheldrüse, sog. Kuttner Tumor wur in der Periode 1965–1971 diagnostiziert. Dieser mor" ist wenig bekannt, nur ungefähr 50 Fälle publiziert. Es ist möglich, dass diese Läsion iel ger ist, als man geglaubt hat. Es ist zu bemerken, diese Läsionen klinisch oft als maligne Verände- en angesehen worden sind. Die Etiologie ist un- bekannt. Die lymphozytische und plasmazelluläre Infiltration und das fibrinoidische Material in dem perivaskulären Raum sprechen für eine autoimmune Pathogenese.

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AMELOBLASTIC FIBROMA

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Abstract The ameloblastic fibroma is a rare benign expansile mixed odontogenic tumour composed of mesenchymal and epithelial constituents. The highest incidence is in the first two decades of life. It is 3–4 times more common in the mandible than in the maxilla (Gorlin & Goldman, 1970) Simple excision or curettage is usually sufficient to effect complete cure. The lesion must be differentiated from ameloblastoma which it may resemble both clinically and radiologically An ameloblastic fibroma in a newborn infant is described.

The ameloblastic fibroma or soft mixed odontoma is a relatively uncommon odontogenic mixed tumour composed of both mesenchymal and epithelial constituents (Bernier 1960 Gorlin et al., 1961 1963 Cina et al., 1961 1964 Pindborg, 1965 Gorlin & Goldman, 1970). The ameloblastic fibroma is considered in the first stage in a chain of development in which the ameloblastic odontoma (partially mineralized) is the intermediate and the complex or composite odontoma (completely mineralized) is the final stage (Pindborg 1965 Forsberg et al. 1961) The tumour usually appears as an asymptomatic swelling in the mandible or maxilla of children and young adults. The surgical removal of such a tumour in an infant aged 1 year is described.

CASE REPORT

History

A male infant, born 3 months prematurely required care in a premature nursery for over 2 months. At the age of 1 month, he was noted to have a tumour of the left side of the mandible The visible part was of the size of a pea. The tumour slowly increased in size and at the age of 8 months there was a bean-sized visible tumour (Fig. 1). Radiological examination (Fig. 2) revealed a 3 cm large cystic tumour mass involving the left molar region of the mandible Two dental anlagen seemed to be incorporated in the lesion. A biopsy then showed angiofibromatous tissue, and it was decided, if possible, to withhold operation until the child was older However the tumour increased rapidly in size and there was a visible portion measuring 18 × 12 mm after another few months, and the radiological examination showed enlargement of the lesion. The cystic tumour now extended from molar region to the articular process of the mandible (Fig. 3).

Course and treatment

When the child was aged 12 months the tumour was surgically removed. Incision was made in the mucosa and the mucoperiosteum overlying the tumour was reflected. Then the tumour could be easily elevated from the bony cavity The only bony part removed was a thin bony bridge in the middle of the cavity. This was necessary for complete removal of the tumour behind the bridge. No residual tumour could then be identified. The incision was closed by primary suture The removed tumour was soft but elastic and was more of

1 Visible tumour at the age of 8 months.

2 Radiological examination at the age of 8 nths showing smooth outline of radiolucent lesion the left mandible.

myxoid appearance than of an angiofibroma. Eighteen months after operation a smooth mandible could be palpated and there was no evidence of recurrence. Radiological examination showed increased density and remodelling of the mandible

Pathology

The specimen removed (Fig. 4) consisted of a multilobulated encapsulated tumour weighing 14 g. Two dental anlagen were identified The cut surface of the tumour was white and glistening, and the consistency rather soft but elastic. On microscopic examination (Fig. 5) there were strands and nests of cuboidal epithelial cells scattered in an abundant fibrous stroma. This is the typical appearance of an ameloblastic fibroma or soft mixed odontoma.

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ɣ 5 Microscopic photo of the ameloblastic fibroma ɔwing epithelial islands in embryonic fibrous concτive tissue.

DISCUSSION

ɔe ameloblastic fibroma is a slow-growing pansile, but not invasive, mixed odontogenic mour which usually does not cause any nical symptoms. It is most commonly located the premolar–molar region of the maxilla the mandible. The tumour consists of ithelial strands and nests in a stroma of ɔrous connective tissue The fibrous compoɛnt may vary from a bulky collagen-produc g mass (which is uncommon) to a loose em-ɔnic structure (as was present in this case) sembling the dental papillae (Bernier 1960) he epithelial component simulates the dental mina (Bernier 1960) and according to uge (1967) is the appearance most closely lated to the root sheath of Hertwig. Unpted teeth may be associated with the mour

In a review of 43 cases Gorlin (Gorlin & Goldman, 1970) found the age ranged from 6 months to 42 years, with an average age of 16 years. There was no sex difference. The tumour was 3–4 times more common in the mandible than in the maxilla. The main dif ferential diagnosis is the ameloblastoma that occurs in an older age group Gorlin, in the same publication, reviewed 1 258 cases of ameloblastoma and found the age range from 21 to 48 years, with an average of 39 years. The stromal component of the ameloblastoma consists of a mature fibrous connective tissue as compared with the scanty embryonic type of stroma seen in the ameloblastic fibroma. The epithelial islands in the ameloblastoma are usually larger There is no difference be tween the radiological appearance of an ameloblastic fibroma and that of an unilocular ameloblastoma, as both tend to be cystic and

3 Microscopic photo of the ameloblas... ring epithelial islands in embryonic f... ne tissue.

DISCUSSION

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with smooth outlines (Sonesson, 1950 Pindborg, 1965 Gorlin & Goldman, 1970)

Simple excision of curettage is usually sufficient therapy Very seldom does the tumour recur and may then be due to incomplete removal (Huebsch & Stephenson 1956 Carr et al., 1970 Gorlin & Goldman, 1970) It must be emphasized that only limited surgery is necessary in the treatment of ameloblastic fibroma in comparison with ameloblastoma where more radical surgery is warranted. Histopathological diagnosis is therefore necessary before disfiguring or mutilating surgery is performed.

ZUSAMMENFASSUNG

Ameloblastische Fibrome sind seltene, gutartige Tumore. Es handelt sich um einen gemischten, odontogenen Tumor aus mesenchymalen und epithelialen Bestandteilen. Die meisten Fälle findet man in den ersten 20 Lebensjahren. Diese Tumore sind im Unterkiefer drei- bis viermal gewöhnlicher lokalisiert als im Oberkiefer Einfache Excision und Ausräumung mit scharfem Löffel genügt gewöhnlich für die vollständige Heilung. Man muss diesen Tumor von einem Ameloblastom unterscheiden — klinisch und röntgenologisch können sie sehr ähnlich sein. Es wird ein „Ameloblastisches Fibrom" eines Neugeborenen beschrieben.

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MASKED SPEECH AUDIOMETRY IN CENTRAL DEAFNESS

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stract Speech tests in the presence of white noise different S/N ratios were carried out upon normal jects and patients with a variety of intracranial ses. In 15 patients with brain stem lesions the ded speech scores were found to be significantly er than those of normal subjects. In some, the was unilateral, in others bilateral. No correlation ld be established however with respect to the el or lateralization of the lesion. In a group of patients with temporal lobe lesions the scores m the contralateral ear were consistently and icantly lower than those from the ipsilateral ear difference was not present in a group of patients h cortical lesions outside the temporal lobe. No r evidence of cerebral dominance emerged from comparison of a group of right- and left-handed mal subjects or patients with unilateral right and temporal lobe lesions.

recent years it has become increasingly arent that elementary pure tone tests ap- ed to the investigation of lesions of the cen- l auditory pathways have little diagnostic ue Neurological lesions at brain stem and tical levels have been studied by means of ariety of threshold audiometric techniques the disappointing result that hearing level her showed no deterioration or if it did, n the deterioration was in no case distin- shable with any certainty from similar de ioration found in lesions of the peripheral eptor They therefore remained useless for rposes of topographic diagnosis. In addition, ventional speech audiometry also fails to w abnormal intelligibility scores in the jority of cases with lesions affecting the ntral auditory pathways.

The fact that these tests have failed to reveal any specific derangements in the presence of brain stem or cortical lesions has led to the development of special methods of in vestigation to assess the function of the auditory centres. These new methods of investiga tion of central auditory disorders can be divided unto two main categories: (1) those which make use of pure tones" presented under special conditions, and (2) those which use specially prepared "speech material"

The specially devised pure tone tests are based on the exclusion, as far as possible, of the cognitive factors which may compromise the validity of speech tests. *Matzker (1957)* used successions of brief tone impulses presented to the two ears, with a difference of arrival time so as to bring out errors in spatial localization, the correct assessment of which would depend on the integration of the two monaural stimuli at the central level. Jerger (1960) studied the loudness balance, or mid-plane localization of a tone, presented separately to each of the two ears with self-adjusted intensity Chocholle (1957) analysed the behaviour of supraliminal tonal hearing in the presence of contralateral stimuli. The same author (1959) investigated reflex reaction times for a monaural supra liminal pure-tone stimulus. None of the pure tone tests so far suggested can be said to have shown particular promise for the purposes of localization. Moreover some of them are difficult to put into execution, or at least somewhat intricate.

Ordinary speech contains a certain amount

of redundant or superfluous information which is unnecessary for complete comprehension by normal subjects. In fact normal individuals may recognize an entire message from a part, even though the remaining parts have not been perceived. On the other hand patients with lesions of the central auditory pathways need all the available information contained in speech to ensure full intelligibility Sensitized or low-redundancy speech tests are therefore, based on the principle of reducing as much as possible the redundant information of speech, making words less easily recognizable and in this way enabling the detection of lesions of the central auditory pathways. The sensitization of speech has been obtained by different methods such as: frequency distortion through the use of filters (Bocca et al. 1954 1955) time-compression or accelerated speech (Calearo & Lazzaroni, 1957) periodic interruption (Bocca et al., 1957), by vocal messages periodically oscillating between one ear and the other or swinging speech (Hennebert 1955 Bocca et al., 1957) the use of lists of words delivered at a high level of intensity (Greiner & Lafon, 1957) and the resynthesis of the two semispectres of the message delivered simultaneously one to each ear (Matzker 1958)

The effect of white noise on the loudness of speech applied to the same ear was found by Pollack (1949) to be a function of the speech-to-noise ratio rather than of the absolute level of the speech alone or of the noise alone That is to say a given speech-to-noise (S/N) ratio produces, approximately a constant depression in the loudness level of speech. Sinha (1969) using a white noise applied simultaneously with words to the same ear at different S/N ratios, found a marked reduction in discrimination in the ear contralateral to temporal lobe lesions. This finding was recently confirmed by Rosenblüt & Oyarce (1971) with a fixed S/N ratio of 6 dB. None of these authors, however have studied this method in subcortical lesions of the central auditory pathways. In the present investigation we have studied the effect of white noise masking on the intelligibility of speech in normal subjects and we have used this procedure as a low-redundancy speech test in the study of patients with lesions at different levels of the central auditory pathways.

MATERIAL AND METHOD

In the investigations to be described a conventional two-channel diagnostic audiometer (Peters AP 5) was used. As a first step pure tone and speech audiometry using several lists each of 25 phonetically balanced, monosyllabic, meaningful words was carried out on all subjects. Subsequently speech intelligibility was studied with the words presented to the patient via earphones at a sensation level of 50 dB (i.e with respect to the average hearing level for the speech frequencies 500, 1 000 and 2 000 Hz) in the presence of white noise masking applied to the same ear at different speech-to-noise ratios. The S/N ratios most commonly used were 0 and +5 dB

The case material comprised 53 subjects, 21 normal individuals and 32 patients with different types of intracranial lesions. Of the latter the majority were in patients from the neuro-surgical department in whom the diagnosis was verified during subsequent operation. Complete investigations were performed in most of the cases, these included neurological examination, pneumo-encephalography ventriculography gamma scan, electro-encephalography and other laboratory examinations.

The patients were classified into the following groups according to the anatomical location of the lesions:

Group 1 Brain stem lesions
Group 2 Temporal lobe lesions
Group 3 Other cortical lesions.

RESULTS

In order to determine the normal speech intelligibility scores in the presence of white noise masking, the method previously described

applied to the group of 21 *normal sub-* ... They were tested at various speech-to- ·ise ratios (−5 0, +5 and +10 dB) and their erage discrimination scores are shown in ble I. The average discrimination score at S/N ratio of −5 dB (20%) was considered low to allow a clinical comparison with ients affected by lesions of the central audi- pathways. At the S/N ratio of +10 dB erage discrimination score of 79%) many rmal subjects obtained speech intelligibility ... very similar to those elicited in the pres- ce of normal, unmasked speech therefore indication was that at this level the mask effect of white noise was insufficiently rked to be of value. It was concluded that S/N ratios of 0 dB (average discrimination re of 43%) and +5 dB (average discrimina n score of 67%) were the more useful ones the purpose of comparison and evaluation with lesions of the central auditory thways.

Of the normal subjects, 12 were right nded. To determine if there was any indica n of cerebral dominance, a comparative dy was made of the average discrimination ... in the right and left ears of both groups. can be seen from Table II, in both right left-handed subjects the discrimination res were slightly better in the right ears at S/N ratios of +5 and +10 dB

brain stem group consisted of 15 pa ... (Table III). Of these 10 cases had brain tumours—8 of them confirmed by opera and the remaining 2 patients (cases 6 and were diagnosed by arteriographic and air lographic studies. Five were cases of ltiple sclerosis.

n 13 of the 15 patients examined the pure thresholds were within normal limits. Of remaining 2 cases, one had a bilateral per deafness probably due to acoustic (case 3) and one showed a slight uni- perceptive deafness (case 8).

In 12 of the 15 cases there were normal ech audiograms for unmasked speech. Of remaining 3 patients, two had normal pure tone thresholds but abnormal speech discrimi- nation in one ear. This abnormality was to the side of lesion in one (case 1) and to the opposite side in the other (case 14). The third patient (case 3) had a bilaterally abnormal speech discrimination in accordance with a bilateral perceptive deafness.

Fourteen of the 15 patients with brain stem lesions had abnormal discrimination scores for masked speech tests, the abnormalities being moderate in 7 cases (with scores ranging from 16 to 24% for the S/N ratio of 0 dB and from 44 to 56% for the S/N ratio of +5 dB) and marked in the other 7 patients (with scores ranging from 0 to 12% for the S/N ratio of 0 dB and from 0 to 40% for the S/N ratio of +5 dB). The average discrimination scores for the brain stem group were 24% for the S/N ratio of 0 dB and 48% for the S/N ratio of +5 dB (the average values for normal subjects being 43 and 67% respectively). Of the 14 cases with abnormal discrimination scores, 3 showed a unilateral deficit and 11 a bilateral deficit in 7 of the latter however the lesion was pre dominantly to one side. In only 1 case (case 8) were all the results for masked speech tests within normal limits.

On the basis of neurological and operative data, it has been established that 7 cases had

Table I. *Normal subjects*

	Speech/noise ratio (dB)			
	−5	0	+5	+10
Average percentage word recognition	20	43	67	79

Table II. *Average percentage word recognition in right and left-handed subjects*

Speech/Noise Ratio (dB)	−5		0		+5		+10	
Ear	R	L	R	L	R	L	R	L
Right-handed	20	20	42	45	77	69	82	78
Left-handed	20	19	42	43	51	61	84	74

of redundant or superfluous information which *is unnecessary for complete comprehension* by normal subjects. In fact normal individuals may recognize an entire message from a part, even though the remaining parts have not been perceived. On the other hand patients with lesions of the central auditory pathways need all the available information contained in speech to ensure full intelligibility. Sensitized or low redundancy speech tests are, therefore, based on the principle of reducing as much as possible the redundant information of speech making words less easily recognizable and in this way enabling the detection of lesions of the central auditory pathways. The sensitization of speech has been obtained by different methods such as: frequency distortion through the use of filters (Bocca et al. 1954, 1955), time-compression or accelerated speech (Calearo & Lazzaroni, 1957), periodic interruption (Bocca et al., 1957), by vocal messages periodically oscillating between one ear and the other or swinging speech (Hennebert, 1955; Bocca et al., 1957), the use of lists of words delivered at a high level of intensity (Greiner & Lafon, 1957) and the resynthesis of the two semispectres of the message delivered simultaneously one to each ear (Matzker, 1958).

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ıble IV *Temporal lobe lesions*

agnosis	scores for normal speech		scores for masked speech S/N ratio 0 dB		scores for masked speech S/N ratio +5 dB	
	Ip.	Con.	Ip.	Con.	Ip.	Con.
Left temporo-occipital astrocytoma, grade III	96	88	32	4	60	40
Left parieto-temporal astrocytoma	100	88	36	16	68	56
Right temporal lobe haematoma	92	92	48	20	76	48
Left parieto-temporal astrocytoma, grade III	92	92	36	4	68	48
Left temporo-occipital astrocytoma, grade IV	100	96	44	44	72	56
Right parieto-temporal astrocytoma, grade III	88	84	40	20	76	52
Right parieto-temporal metastatic epidermoid carcinoma	96	80	40	16	56	36
Left temporal astrocytoma, grade III	84	84	16	20	36	48
Left temporal cholesteatoma	88	80	36	24	64	44
Right temporal lobe haematoma	92	84	44	12	72	[illegible]

ıs case presented a unilateral perceptive afness). Three cases with bilateral brain stem ᴧons had unilateral or mainly unilateral abrmal discrimination scores. In another case th a prevalently unilateral brain stem lesion ase 6) bilaterally abnormal masked speech st results were obtained.

Of the 4 cases with pontine lesions, 2 had arkedly abnormal masked speech test results d in the remaining 2 patients the abnormalis were moderate. In all of these 4 cases the ᴧon was unilateral and in 3 of them the asked speech abnormalities were also unieral (the abnormalities were obtained in the r corresponding to the side of the lesion in e case and in the opposite side to the lesion the remaining two cases). In the fourth case masked speech test results were bilaterally normal.

Of the 5 cases with bulbo-pontine lesions, 3 d markedly abnormal speech test results and the remaining 2 patients the abnormalities re only moderate. Three of the cases had ılateral or prevalently unilateral brain stem ions: in 2 of them the abnormalities were ore marked in the ear corresponding to the e of the lesion and in the remaining case the abnormalities were present in the ear opposite to the lesion.

The only case with a strictly bulbar localization (case 10) had a bilateral brain stem lesion and the abnormalities for masked speech tests were moderate and bilateral.

It follows from this analysis that no clear pattern is apparent as to the relationship between the side of the lesion or its longitudinal level in the brain stem and the masked speech test results.

The individual results for the masked speech scores in normal subjects and in patients with brain stem lesions are presented to the left and right of Fig. 1 respectively. In each the full line curve is the average for the normal subjects. Although there is a somewhat wide scatter of results, the standard deviation of the normal group being 12.7% at S/N 0 dB and 11.5% at S/N +5 dB nevertheless it is immediately apparent that there is a marked difference between the two groups, the majority of the intelligibility scores from patients with brain stem lesions falling well below the curve representing the average values for normal individuals.

The *temporal lobe lesions group* consisted of

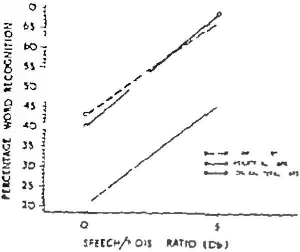

Fig 2

10 patients (Table IV) in all of whom the diagnosis was confirmed by operation. Eight cases had temporal lobe tumours (their histological nature was determined by biopsy) and the remaining 2 (cases 3 and 10) had subdural temporal lobe haematomas. Five cases were examined pre-operatively and the remaining 5 patients were tested during the first 10 days after the operation.

In 8 of the 10 patients with temporal lobe lesions, the pure tone thresholds were within normal limits. Of the remaining 2 cases, one (case 6) had a slight unilateral conductive deafness and the other (case 8) had a high tone perceptive deafness in the ear ipsilateral to the lesion and a moderate conductive deafness in the contralateral ear

Nine cases showed normal speech audiograms for unmasked speech. Only 1 patient (case 8) had a definite abnormality for unmasked speech, the abnormality being confined to the ear ipsilateral to the lesion. An analysis of the intelligibility scores for unmasked speech at 50 dB sensation level (Table IV) reveals that in 7 out of 10 cases (cases 1 2, 5 6, 7 9 and 10) there was a slight difference between the two ears, showing poorer scores in the ears contra lateral to the lesions. However the difference was not sufficiently marked to be of clear diagnostic value.

By contrast the results for masked speech were clearly significant. In nearly all the cases observed, the intelligibility scores for masked speech at the two ears were markedly asymmetric, *the scores being significantly lower in the ears contralateral to the lesions.* In these ears the intelligibility scores ranged from 1? to 24% at the S/N ratio of 0 dB and from 32 to 56% at the S/N ratio of +5 dB. In the ears homolateral to the lesions the scores were within normal limits. Two cases need special mention. In case 5 despite the results between the two ears being asymmetric at the S/N ratio of +5 dB, this pattern failed to appear at the S/N ratio of 0 dB where the intelligibility scores of both ears were identical, as a result of this finding the S/N ratio of −5 dB was investigated and a poorer score was obtained from the ear contralateral to the lesion (4%) in comparison to the ipsilateral ear (18%). In case 8 it was not possible to demonstrate this asymmetry in the results for the two ears. The reason for this lies in the presence of a perceptive deafness in the ear ipsilateral to the lesion which, in itself gave rise to very poor discrimination scores even for normal (unmasked) speech however in the presence of white noise masking poor intelligibility scores were obtained in the ear contralateral to the lesion and these figures (20 % at the S/N ratio of 0 dB and 48% at the S/N ratio of +5 dB) were in good agreement with the scores obtained from the rest of the patients.

The average scores at the S/N ratios of 0

Table V *Average percentage word recognition in right and left temporal lobe lesions*

	Average scores for masked speech			
	S/N ratio 0 dB		S/N ratio 5 dB	
	Ip	Con.	Ip	Con.
Right temporal lobe lesions	43	17	70	[illegible]
Left temporal lobe lesions	35	17	65	[illegible]

able VI *Other cortical lesions*

agnosis	.. scores for normal speech		.. scores for masked speech			
			S/N ratio 0 dB		S/N ratio +5 dB	
	Ip.	Con.	Ip.	Con.	Ip.	Con.
Left fronto-parietal oligodendroglioma, grade II	84	76	12	24	44	56
Right frontal meningioma	96	100	40	24	56	64
Right parietal astrocytoma, grade III	92	80	28	52	68	[illegible]
Right parietal meningioma	100	96	36	24	48	52
Left fronto-parietal astrocytoma	100	100	32	44	68	92
Left parietal tumour	100	96	32	20	40	48
Left parietal angioma	80	70	16	3?	48	60

B and +5 dB for these cases are shown in ig. 2 together with the normal averages as ference The contralateral-ipsilateral differ nces are clearly apparent.

In order to ascertain if there was any sugestion of cerebral dominance we compared e masked speech test results between the ame sides, i.e. ipsilateral and contralateral, in ght and left temporal lobe lesions. As can be en from Table V no clear differences merged apart from slightly higher scores in e ipsilateral ears of the right temporal lobe sions while this tendency seemed to be reersed in the contralateral ears.

The group of patients with *cortical lesions utside the temporal region* consisted of 7 ases with tumours of different localizations able VI) Six of them were confirmed by peration. All these cases had normal pure one and speech audiograms. Masked speech sts showed that, in contrast to temporal lobe sions, *no clear pattern emerged from the omparison between the two ears.* In fact, in cases (cases 2, 3 4 and 6) the tendency obrved at the S/N ratio of 0 dB was opposite that at the S/N ratio of +5 dB. In the maining 3 cases (cases 1 5 and 7) the in lligibility scores were better in the ears conalateral to the lesions at both S/N ratios. In o case were poorer scores demonstrated in e contralateral ear at both S/N ratios.

DISCUSSION

It will be recalled that of our group of 10 patients with temporal lobe lesions, 7 had slightly poorer intelligibility scores in the ears contra lateral to the lesions with normal, unmasked speech. A similar finding has been reported by Bocca et al. (1955) with lists of disyllabic words. Goldstein et al. (1956) found a discrimination loss in the contralateral ears of 4 cases of left hemispherectomy when rather difficult lists of words (Rush Hughes PB s) were used and Rosenblüt & Oyarce (1971) reported similar re sults with lists of monosyllables. All the previous observations tend to suggest that the contralateral defect brought about by temporal lobe lesions may be demonstrated even with normal speech when difficult" material is used (monosyllables, Rush Hughes PB s, etc.) However with easy" speech (spondees, sentences, W 22 PB's) this contralateral deficit is not apparent.

The contralateral discrimination deficit in temporal lobe lesions only vaguely suggested when difficult" normal speech material is used, becomes clearly evident when white noise masking is added to the speech. However it is noteworthy in this respect that this type of asymmetry was not observed in a group of patients with cortical lesions not affecting the auditory cortex, that is to say outside the

temporal lobe. The fact that in this latter group the intelligibility scores were usually slightly worse than those found in normal subjects might be explained by the fact that all of these patients had some degree of increased intracranial pressure. Antonelli et al. (1963), Calearo (1960) and Calearo & Lazzaroni (1957) reported low intelligibility scores when this condition was present and explained the impaired discrimination in terms of a temporary diminution of the intellectual capacity of the patient.

According to Bocca et al. (1955) the loss of discrimination in the contralateral ears of temporal lobe lesions tends to disappear about 20 to 30 days after the surgical removal of the affected temporal cortex, as a result of a compensation mechanism. This phenomenon would explain the absence of a discrimination loss in the contralateral ears of some of their cases of temporal lobectomies. Unlike these findings, in nearly all our cases with temporal lobe lesions a marked discrimination loss in the ears contralateral to the lesions was present. The explanation for the difference between our findings and those of Bocca seems to be twofold (*a*) all our cases were examined within 10 days of the operation too short a period for the compensation mechanism to take place (*b*) in those cases tested postoperatively temporal lobe lesions were not removed but only biopsied. The analysis of our findings in comparison with those reported by Bocca et al. (1955), appears to suggest that the contralateral discrimination loss exists only when the function of one cortical auditory area is impaired, disappearing later on when the affected area has been completely "removed" and the healthy contralateral ear is able to counterbalance the function of the missing zone.

It is well known that the left cerebral hemisphere of right handers is the dominant one for the whole complex of mechanisms of speech regulations. Penfield & Roberts (1959) have shown further that the left dominance, as far as speech is concerned, is present not only in right handed but even in the majority of left handed subjects. In the circumstances certain differences might be anticipated in the results from right and left-handed normal subjects. However mention has already been made of the fact that no differences were apparent either in normal subjects or indeed in patients with unilateral right and left temporal lobe lesions. In this respect our results agree with those of Calearo & Antonelli (1963) who found that the contralateral discrimination loss was more or less of the same order whether the lesion was located in the right or in the left temporal lobe Our findings, therefore, seem to indicate that the cortical integration of the auditory message is a symmetrical and equivalent function in the two temporal lobes.

The masked speech test results from the brain stem and temporal lobe lesions groups differ mainly in the fact that the discrimination loss was frequently bilateral in the brain stem group but always unilateral in the temporal lobe group. The explanation for this may be that in the brain stem the hearing pathways on both sides are concentrated in a limited space, whereas in the cortex they spread out and become completely separated in the two hemispheres. As a result, a lesion of a similar extent in the brain stem may affect a much larger portion of the auditory tract than in the cortex, thus producing a much higher incidence of severe and bilateral impairment. The unilateral discrimination loss in temporal lobe lesions makes the comparison of the masked speech test results between the two ears in itself a tool of unquestionable diagnostic value. However since the masked speech scores in brain stem lesions were often bilaterally depressed, any diagnostic significance attaching to them rests on our ability to recognize departures from normality Here certain difficulties are apparent since although the majority of our patients with brain stem lesions had much poorer scores than the average normal, a number of these were comparable with those at the lower end of the normal discrimination range This fact imposes certain diagnostic limits upon the test as applied in

rain stem lesions and indicates the desirability of further studies in the selection of the word material aimed at reducing the normal discrimination range and thus making possible a clearer distinction between both groups. Although similar results to the above have been reported by Antonelli et al. (1963) and Calearo & Antonelli (1968) using distorted, alternated and accelerated speech the essential feature in all is the removal by one means or another of redundant information in normal speech.

In this respect speech masked by white noise has the merit of extreme simplicity and calls for neither elaborate machinery or sophisticated techniques. Its effectiveness may be gauged from the fact that the results reported here, while possibly superior are by no means inferior to those reported by others. As a valuable diagnostic tool, therefore for the detection of central lesions of the auditory pathways, it would seem to be within the capabilities of any centre equipped with minimal audiological facilities.

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Thanks are due to the physicians and surgeons of the National Hospital, Queen Square, for permission to examine these patients and to Dr J D Hood, Director of the Medical Research Council Hearing and Balance Unit, for his advice and help throughout this study

ZUSAMMENFASSUNG

Sprachteste im Zusammenhang weißen Lärmes mit unterschiedlichen Sprach–Lärm-Proportionen wurden an Gesunden sowie an Patienten mit verschiedenen intrakraniellen Läsionen ausgeführt. Die maskierten Sprachteste von 15 Patienten mit Hirnstammläsion waren signifikant niedriger als diejenigen der Gesunden. Bei einigen war der Verlust unilateral, bei anderen bilateral. Es konnte jedoch keine Korrelation in Hinsicht Höhe oder Seite der Läsion erhoben werden. In einer Gruppe von 10 Patienten mit Temporallappenläsionen waren die Werte des kontralateralen Ohres immer und signifikant niedriger als diejenigen des ipsilateralen Ohres. Diese Differenz war bei einer Gruppe von Patienten mit kortikalen Läsionen außerhalb des Temporallappens nicht vorhanden. Der Vergleich einer Gruppe normaler Rechts- und Linkshänder oder von Patienten mit unilateraler rechts- und linkseitigen Temporallappenläsionen läßt keine Evidenz zerebraler Dominanz erkennen.

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IMMUNELEKTROPHORETISCHE UNTERSUCHUNG ZUR EIWEIßVERTEILUNG IN DER MEERSCHWEINCHEN PERILYMPHE NACH SCHALLBELASTUNG

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(Eingegangen am 7 März, 1972)

*Ausz*treit. Das Proteinmuster von Meerschweinchen-*P*erilymphe wurde bei Normaltieren und nach *ge*hörschädigender Schallbelastung immunelektrophore*ti*sch untersucht. In 4 μl blutfreier Perilymphe waren *b*is zu 5 Komponenten nachweisbar: Albumin und je *ei*ne Komponente im α-, β_1-, β_2- und γ-Globulinbe*r*eich. Die γ- und besonders die β_2-Globulinlinien tra*te*n nur sehr schwach und nicht in allen Fällen auf. *I*n 1 2 μl Perilymphe zeigten sich stets noch Albumin *u*nd β_1-Globulin. α- und besonders γ-Globulinlinien *t*raten nicht mehr regelmäßig auf, die β_2-Globulinlinie *fe*hlte ganz. Plasmaverunreinigungen bis zu 0,2 und *a*rterielle Perfusion der Tiere mit Ringer Lösung *v*eränderten die Ergebnisse nicht. Das Proteinmuster *v*on vestibulärer und tympanaler Perilymphe ist qua*li*tativ identisch. Der Gesamtproteingehalt scheint in *v*estibulärer Perilymphe höher zu sein als in tympana*le*r Nach Schallbelastung von 10 kHz, 135 dB, 1 *S*tunde war weder sofort noch im Zeitraum der darauf *fo*lgenden 4 Tage eine qualitative Veränderung des *P*roteinmusters in der Perilymphe nachweisbar

*O*bwohl die Eiweiße zu den häufig untersuch*te*n chemischen Stoffklassen in den Innenohr*fl*üssigkeiten gehören, zeigen die vorliegenden *E*rgebnisse wenig Übereinstimmung, weder *h*insichtlich der qualitativen noch der quanti*t*ativen Aussagen. Ein besonderes Problem *is*t die bei der Entnahme der Proben mögliche *V*erunreinigung mit Blut. Der hohe Plasma*ei*weißgehalt kann die Ergebnisse erheblich *v*erfälschen.

Für die qualitative Untersuchung der Eiweißverteilung ist die Immunelektrophorese die zur Zeit empfindlichste Mikromethode. Wegen der hohen Nachweisempfindlichkeit und Trennwirkung ist dabei die Anforderung an die Reinheit der zu untersuchenden Innenohrflüssigkeiten besonders hoch. Das Ergebnis hängt außerdem entscheidend von den angewendeten immunologischen Bedingungen ab. Wir haben unter besonderer Berücksichtigung der Fehlermöglichkeiten die Eiweißverteilung in der Meerschweinchen-Perilymphe und deren mögliche Veränderung durch Schallbelastung mit Hilfe der Immunelektrophorese untersucht. Es wird nachfolgend über die Durchführung und die Ergebnisse berichtet.

MATERIAL UND METHODEN

Gewinnung und Reinheitskontrolle der Perilymphe

Die Gewinnung der Perilymphe erfolgte durch Punktion der knöchernen Schneckenkapsel der Basalwindung unmittelbar bzw bei mit Ringer Lösung perfundierten Tieren 15–30 Minuten post mortem. Nach Entfernen der Mittelohrschleimhaut wurde der Labyrinthknochen über der Scala vestibuli, der Scala tympani bzw dem Helicotrema perforiert und die Perilymphe nach Aufsetzen einer silikonisierten Glaskapillare die vorn mit einem kurzen Stück dünnen Silikongummischlauch (Innendurchmesser 0,5 mm) versehen war

*D*iese Ergebnisse wurden im Auftrage des Ministe*ri*ums für Gesundheitswesen der DDR im Rahmen *de*r Lärmschadenforschung erarbeitet.

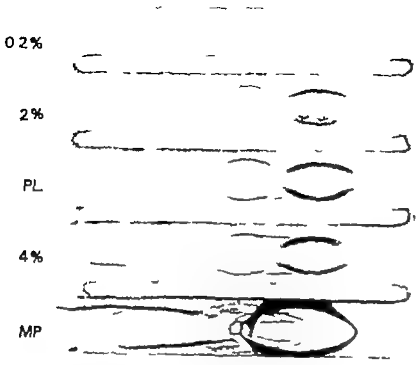

Abb 2 Immunelektropherogramme von je 4 µl Meerschweinchenplasma-Verdünnungen (0,2, 2 u. 4%ig), unverdünntem Meerschweinchenplasma (MP) und reiner Perilymphe (PL)

In einer weiteren Versuchsreihe ($N = 12$) wurde die Perilymphe aus den beiden Schneckenscalen getrennt untersucht. Dabei zeigten sich, unbeeinflußt durch die Beschallung in den meisten Fällen sowohl bei der vestibulären als auch bei der tympanalen Perilymphe die gleichen 4 Präzipitationslinien wie bei der Untersuchung der Gesamtperilymphe. Die 5 Li- im β_2-Globulinbereich trat auch hier nur inzelt und wenn, dann stärker in der tympanalen als in der vestibulären Perilymphe auf Die β_2-Globulinkomponente scheint demnach in der tympanalen Perilymphe in höherer Konzentration vorhanden zu sein als in der vestibulären Perilymphe

Immunelektrophorese von Plasmaverdünnungen und Perilymphe (4 µl) nicht perfundierter Tiere ($N = 12$)

Um auszuschließen daß die Perfusion das Eiweißmuster der Perilymphe beeinflußt wurden den Perilymphproben von nicht perfundierten Tieren mit untersucht.

Da bei der Perilymphe nicht perfundierter Tiere mit Blutverunreinigungen zu rechnen war wurde in einer weiteren Versuchsreihe der Einfluß von Blutverunreinigungen auf das immunelektrophoretische Bild kontrolliert. Dazu wurden verschiedene Verdünnungen von Meerschweinchenplasma untersucht und die Ergebnisse mit denen von reiner Perilymphe verglichen. Die Abb 2 zeigt einen Vergleich solcher Immunelektropherogramme. Bei 0,2%igem Plasma ist nur die Albuminlinie schwach angedeutet. Plasmaverunreinigungen bis zu etwa 0,2% verändern also die Ergebnisse kaum 2–4%iges Plasma gibt dagegen schon ähnliche Elektropherogramme wie die Perilymphe.

Da bei den nicht perfundierten Tieren der Blutgehalt der tympanalen Perilymphe meist über 0,2% lag wurde hier oft nur die vestibuläre Perilymphe untersucht. Die tympanale Perilymphe wurde nur dann in die Untersuchung mit einbezogen wenn ihr Blutgehalt < 0,2% betrug. Die Abb 3 zeigt eine Gegenüberstellung entsprechender Immunelektropherogramme Die Ergebnisse sind insgesamt gleich mit denen von perfundierten Tieren. Das Eiweißmuster der Perilymphe wird also durch die Perfusion der Tiere qualitativ nicht verändert.

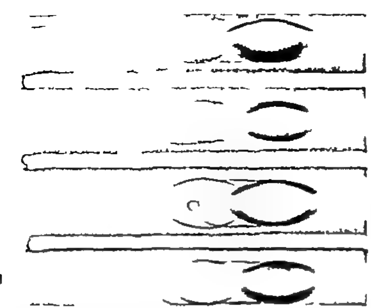

Abb. 3. Immunelektropherogramme von je 4 µl vestibulärer (*a, c*) und tympanaler (*b, d*) Perilymphe eines unbeschallten (*a, b*) und eines beschallten (*c, d*) Ohres von einem nicht perfundierten Tier.

nmunelektrophorese von Perilymphe (1–2 µl) zu verschiedenen Zeiten nach der Be ellung (135 dB) entnommen wurde

eine Schallbelastung möglicherweise erst einer bestimmten Latenz das Proteinspek um in der Perilymphe verändert, erfolgte in nteren Untersuchungsreihen die Perilymphntnahme zu verschiedenen Zeiten nach Be hallungsende (Tab. 1). Um mögliche qualita ve Unterschiede, insbesondere im Globulinreich, besser zu erkennen, wurden außerdem mmunelektrophoretisch untersuchten Pe lymph-Mengen zunächst auf 2 µl und dann f 1 µl reduziert.

Es zeigte sich, daß auch bei kleinen Perilymph-Mengen (1–2 µl) (Abb. 4) außer Albumin noch die α- und β_1-Globulinkomponente als feine Linien nachweisbar sind. die α-Globulinlinie trat jedoch bei tympanaler Perilymphe nicht mehr in allen Fällen auf. Die γ-Globulinlinie war nur noch bei vestibulärer Perilymphe in einigen Fällen angedeutet. Die β_2-Globulinlinie fehlte bei den 2 µl-Proben ganz. Ein qualitativer Unterschied im Proteinmuster der Perilymphe von beschallten und unbeschallten Ohren war auch unter diesen veränderten Versuchsbedingungen nicht nachweisbar.

Bei 1 µl-Perilymphproben ließen sich gewisse quantitative Unterschiede besser erkennen als bei Verwendung größerer Perilymphmengen.

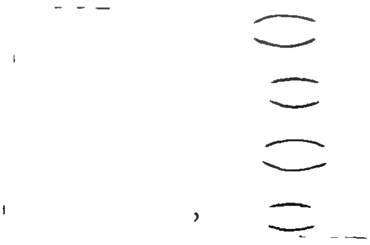

Abb. 4. Immunelektropherogramme von je 2 µl vestibulärer (*a, c*) und tympanaler (*b, d*) Perilymphe eines unbeschallten (*a, b*) und eines beschallten (*c, d*) Ohres.

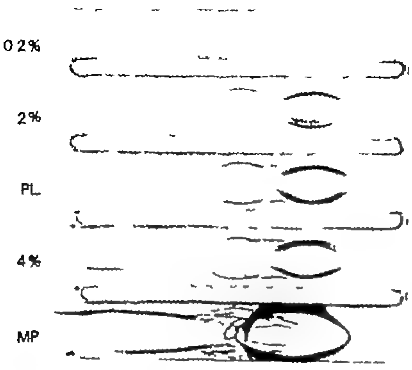

Abb. 2. Immunelektropherogramme von je 4 µl Meerschweinchenplasma-Verdünnungen (0,2, 2 u. 4%ig), unverdünntem Meerschweinchenplasma (MP) und reiner Perilymphe (PL).

In einer weiteren Versuchsreihe ($N = 12$) wurde die Perilymphe aus den beiden Schneckenscalen getrennt untersucht. Dabei zeigten sich, unbeeinflußt durch die Beschallung, in den meisten Fällen sowohl bei der vestibulären als auch bei der tympanalen Perilymphe die gleichen 4 Präzipitationslinien wie bei der Untersuchung der Gesamtperilymphe. Die 5. Linie im β_2-Globulinbereich trat auch hier nur vereinzelt und wenn, dann stärker in der tympanalen als in der vestibulären Perilymphe auf. Die β_2-Globulinkomponente scheint demnach in der tympanalen Perilymphe in höherer Konzentration vorhanden zu sein als in der vestibulären Perilymphe.

Immunelektrophorese von Plasmaverdünnungen und Perilymphe (4 µl) nicht perfundierter Tiere ($N = 12$)

Um auszuschließen, daß die Perfusion das Eiweißmuster der Perilymphe beeinflußt, wurden Perilymphproben von nicht perfundierten Tieren mit untersucht.

Da bei der Perilymphe nicht perfundierter Tiere mit Blutverunreinigungen zu rechnen war, wurde in einer weiteren Versuchsreihe der Einfluß von Blutverunreinigungen auf das immunelektrophoretische Bild kontrolliert. Dazu wurden verschiedene Verdünnungen von Meerschweinchenplasma untersucht und die Ergebnisse mit denen von reiner Perilymphe verglichen. Die Abb. 2 zeigt einen Vergleich solcher Immunelektropherogramme. Bei 0,2%igem Plasma ist nur die Albuminlinie schwach angedeutet. Plasmaverunreinigungen bis zu etwa 0,2% verändern also die Ergebnisse kaum. 2–4%iges Plasma gibt dagegen schon ähnliche Elektropherogramme wie die Perilymphe.

Da bei den nicht perfundierten Tieren der Blutgehalt der tympanalen Perilymphe meist über 0,2% lag, wurde hier oft nur die vestibuläre Perilymphe untersucht. Die tympanale Perilymphe wurde nur dann in die Untersuchung mit einbezogen, wenn ihr Blutgehalt <0,1% betrug. Die Abb. 3 zeigt eine Gegenüberstellung entsprechender Immunelektropherogramme. Die Ergebnisse sind insgesamt identisch mit denen von perfundierten Tieren. Das Eiweißmuster der Perilymphe wird also durch die Perfusion der Tiere qualitativ nicht verändert.

ben mit hämolytischem Blut erkennt man nach dem Zentrifugieren und kann sie verwerfen. Eine mögliche Verunreinigung der Perilymphe mit Gewebsflüssigkeit wird bei der Blutbestimmung nicht mit erfaßt. Sie ist jedoch bei der von uns angewendeten Entnahmetechnik we nig wahrscheinlich. Wir glauben deshalb daß die von uns gefundenen 5 Komponenten wirk lich Perilymphproteine sind und daß sich deren Zahl bei Verwendung größerer Perilymphmengen noch erhöhen kann.

Unsere Beobachtung, daß der Gesamtproteingehalt der vestibulären Perilymphe höher zu sein scheint als der der tympanalen Perilymphe, stimmt mit quantitativen Angaben von Rauch (1964) und Silverstein (1966) beim Meerschweinchen bzw bei der Katze überein.

Die in der Arbeit von Beck & Holz (1966) abgebildeten Immunelektropherogramme lassen vermuten daß die untersuchte Perilymphmenge, die nicht angegeben wurde, zumindest bei den unbeschallten Tieren zu gering oder (und) das Perilymph-Antiserum-Verhältnis nicht optimal war Es ist zu erwarten, daß auch bei unbeschallten Tieren bei einer größeren Menge gefrierpräparierter Perilymphe unter optimalen immunologischen Bedingungen Globulinkomponenten nachweisbar sind. Damit wurde eine Diskussion über einen qualitativen Unterschied im Proteinmuster der Perilymphe beschallter und unbeschallter Tiere entfallen der auch von anderen Autoren (Miyake 1960 Komarovich & Plouzhnikov 1966) bei der Elektrophorese von Meerschweinchen- bzw Katzen-Perilymphe nicht gefunden wurde Eine eindeutige Aussage über quantitative Änderungen des Gesamtproteins in der Perilymphe nach Schallbelastung kann bisher nicht gemacht werden.

SUMMARY

The composition of proteins in the perilymph of guinea pigs (normal and noise-deafened animals) was investigated immunoelectrophoretically I 4 µl of blood-free perilymph up to 5 components were detected; albumin, α- β_1- β_2- and γ-globulin The and especially the β_2-globulin bands were barely visible and did not occur in all the cases. However in 1–2 µl of perilymph albumin and β_1-globulin were always found. α- and especially γ-globulin bands occasionally disappeared, the β_2-globulinband being entirely absent. Contamination of perilymph with plasma up to 0 2 per cent and arterial perfusion of the animals with Ringer solution did not alter the results The qualitative composition of proteins in the perilymph of the scala tympani and vestibuli is identical. Total protein seems to be higher in the perilymph of the scala vestibuli than in the scala tympani. Acoustic stimulation with 10 KC, 135 dB, for 1 hour did not cause a qualitative change in the protein composition of the perilymph within 4 days following the procedure.

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THE PHYSIOLOGICAL RANGE OF PRESSURE DIFFERENCE AND CUPULA DEFLECTIONS IN THE HUMAN SEMICIRCULAR CANAL

Theoretical Considerations

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Abstract The question of what constitutes the "physiologic" behavior of the cupula has been the subject of debate for some time. Calculations are presented which suggest that the cupula constitutes a biological pressure transducer with a threshold of the same order of magnitude as that of the auditory system. This indicates that it would probably be extremely easy to traumatize the cupula by exposing it to pressure gradients far beyond its normal dynamic range in the course of experimental preparations intended to visualize cupula motion. An estimate of the dynamic range of cupula motion may also be obtained which indicates that the center of the cupula may move as little as ten millimicrons at the 0.1 deg sec² acceleration levels commonly associated with behavioral ...de. Accelerations of 30 deg sec² or sudden ...ty changes of 600 deg sec, typical of maximal ...induced head motions should produce cupula ...point motions no greater than about three microns. ... of the small dynamic range of cupula motions, modes of cupula deflection other than rotation about the crista cannot be ruled out, because they are indistinguishable from a dynamic point of view.

Recently there has been an increase of research interest in the histology of the attachment of the cupulae, otolithic and tectorial membranes to the sensory cell areas, and renewed effort to consider the exact nature of the mechanical stimulus to hair cells. In particular there has been increasing speculation that the response of the semicircular canal cupula to angular acceleration may consist of displacement of the structure as a whole instead of or in addition to deflection bending. The generally accepted concept of cupula motion is based on the classical preparation of Steinhausen (1931) in the pike, in which the cupula was seen to deflect like a swinging door within the ampulla, in response to directly applied pressure stimulus. It is often tacitly assumed that gross motions of the cupula within the ampulla typify the physiologic behavior of this structure. However this concept, although teleologically attractive because of the particular morphology of the ampulla, may not necessarily be valid.

Steady state cupula pressure difference

A pressure difference occurs across the cupula when endolymph in the canal is accelerated. The resulting force on the cupula can be created either by an angular acceleration stimulus normal to the plane of the canal, or by natural or artificially created density gradients in the endolymph ring due to temperature gradients across the canal.

Since the density and temperature coefficient of expansion of endolymph are known and the morphology of the membranous canals have been extensively studied, one can calculate the pressure gradient across the cupula in the steady state for both the caloric and acceleration stimuli.

The fundamental assumption which differentiates Steinhausen's torsion pendulum theory of semicircular canal response from the previous Mach-Bruer-Crum Brown hypothesis is that if a constant stimulus torque is imposed on the ring of endolymph counter torques will eventually build up, due to cupula deflection, which ultimately balance the stimulus torque. This will result in some steady state displacement or bending of the cupula. While the magnitude of this displacement depends on cupula stiffness and the mode of its deflection (linear angular or both) the steady state pressure difference is directly related to the stimulus torque and is independent of assumptions made about the cupula motion. It is also independent of the source and magnitude of the viscous countertorques which result from endolymph motion. The only assumptions required to calculate the steady state pressure difference concern the moment f inertia of the ring of endolymph, and the surface area of the cupula.

When the head is turned so that, say the horizontal semicircular canal is stimulated, what volume of endolymph is effected? This has been the subject of some discussion (Groen 1961 Money et al. 1971) but it does not seem unreasonable to model the canal duct as a orus of large radius R and small radius a, as shown in Fig. 1 The increased volume in the utricle and the ampulla may be approximated by a two radian section of a torus whose large and small radii are equal to the radius of the cupula B. Hence

$$\text{lembranous canal volume} \simeq 2\pi^2 a^2 R + 2\pi B^3 \quad (1)$$

Igarashi's (1966) study suggests that representative values for the human morphology re $a = 0.015$ cm, $B = 0.06$ cm and $R = 0.3$ cm This indicates that the utriculo-ampullary olume is approximately equal in man, to the olume of fluid in the horizontal canal duct. herefore,

$$\text{anal volume} \simeq 2\pi^2 FRa^2$$

here $F \simeq 2$ in humans.

It is possible that the utricular volume has been underestimated somewhat, i.e. F is possibly greater than the value of 2.0 assumed here. However it is not clear how utricular volume should be partitioned, and it is hard to see how errors in K of 20–30% could materially effect the fundamental conclusions reached

The moment of inertia of the endolymph ring about the center of the canal duct is therefore given by

$$\Theta \simeq 2\varrho\pi^2 Fa^2 R^3 \quad (3)$$

where the assumption is made that the radius of gyration of the endolymph is approximately the torus radius (R) and ϱ is the density of endolymph. In the steady state, since the acceleration of the endolymph eventually equals the acceleration of the head after a step stimulus, the torque balance equation is:

$$\Theta\alpha = \pi B^2 PR \text{ (steady state)} \quad (4)$$

where: α = angular acceleration of the head (rad/sec²)

P = pressure difference across cupula (dyne/cm²)

The steady state relation of cupula pressure to head acceleration in the plane of the canal is therefore

$$\frac{P}{\alpha} \simeq \frac{2\varrho\pi Fa^2 R^2}{B^2} \quad \frac{\text{dyne sec}^2}{\text{rad cm}^2} \quad (5)$$

Calculation of cupula pressure at acceleration threshold

To calculate the steady state pressure drop across the cupula for subjective threshold, one need only select a reasonable acceleration level for such threshold. Observed values of behavioral thresholds to constant angular acceleration vary widely over the range 0.035 deg/sec² to greater than 2 deg/sec² The literature in this area is reviewed by Clark (1967) The wide variation in results is attributable partly to inter-subject variance and partly to differences in experimental protocol. The subjective

thresholds vary over the widest range. Oculogyral illusion (OGI) probably is the most sensitive behavioral indicator of vestibular function. Oosterveld (1970) was able to provoke OGI in two of his five subjects at angular accelerations of 0.036 degrees/sec². This is roughly consistent with the lowest subjective threshold reported by Mann & Ray (1956) in four subjects. Meiry (1965) found subjective thresholds (75% identification in 3 subjects) to vary from 0.1 to 0.2 deg/sec² with a mean of 0.14 deg/sec². Nystagmus thresholds seem to be slightly more consistent, but higher in value. Buys (1937) and Buys & Rijlant (1939) report 0.8 deg/sec². Montandon & Russbach (1955) and Montandon et al. (1971) indicate similar values.

It is not clear what acceleration levels ultimately reflect the physical threshold of motion of the cupula-endolymph system, or if this is even a meaningful question. It seems reasonable to assume, however, that accelerations of 0.1 deg/sec² are a sufficient stimulus to produce behavioral responses in a substantial percentage of the normal population. Adopting this value as typical of subjective thresholds, one obtains:

$$P_{\text{subjective threshold}} = 2\pi\eta F a^2 R^2 B^{-1} \alpha =$$

$$= 1.25 \times 10^{-4}\ \frac{\text{dyne}}{\text{cm}^2} \qquad (6)$$

One would expect that nystagmus would not be elicited until $P_{\text{nystagmus threshold}} = 10^{-3}$ dyne cm² since nystagmus acceleration thresholds are roughly eight times greater than the assumed subjective threshold.

The threshold pressure difference across the cupula can be estimated independently by considering the pressure and torque involved in caloric stimulation. The figure of 10^{-3} dyne/cm² for nystagmus pressure threshold can be shown to be consistent with Steer et al.'s (1967) calculations of the torque induced on the canal in a uniform temperature gradient field (Oman & Young, 1972).

These calculations can be put in some perspective by the following considerations:

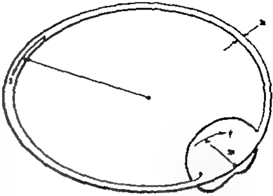

Fig. 1. Assumed hydromechanical model for semicircular canal.

The subjective threshold value of 10^{-4} dyne/cm² constitutes an extremely small pressure. In the normal physiological range of head motions, sustained acceleration greater than 30 degrees/sec² are only rarely encountered, although brief acceleration impulses of up to 600 degrees/sec are often associated with step changes in angular velocity of the head (Hallpike & Hood, 1953). Steady cupula pressure differences should only rarely exceed 3.8×10^{-2} dyne/cm² (less than 4×10^{-5} cm water). The brief moments of high inertial reaction torque associated with impulses of acceleration are balanced almost entirely by the endolymph viscous torques, and not by pressure drop across the cupula.

This result suggests that procedures which involve subjecting the cupula to pressures very much in excess of 10^{-4} cm water for more than the briefest instant might well move the cupula far beyond its normal dynamic range of motion, and that damage to the cupula-crista attachment might possibly result. We feel this possibility should be carefully considered when evaluating experiments aimed at visualizing the motion of the cupula by the injection of stain, ink, or histological studies in which the membranous wall was punctured in preparation.

Physiological range of cupula deflection

Since the preceding calculations suggest that the semicircular canal's sensory areas are

enormously sensitive to pressure gradients, one can only assume that experiments directed at observing the range of cupula motions directly by fenestration might easily traumatize the cupula. Unfortunately the cupula is practically invisible under bright field microscopy

However the theoretical model for the canal hydrodynamics can provide a useful estimate of the range of cupula motion. It will be shown that hydrodynamic models which assume that the cupula swings about its crista imply that the actual physiologic range of cupula motions is sufficiently small as to make a small angle approximation valid. the volume swept out by a swinging cupula is practically identical to that obtained by linear displacements of the cupula, although the resulting hair bundle bending angles are vastly larger for a sliding cupula (Dohlman, 1971). In other words, it can be shown that if the dynamics of the cupula endolymph system are second order calculated values of the short time constant of the canal, and observed values of the long time constant imply cupula deflections sufficiently small as to render the dynamic model insensitive to whether the cupula rotates about the crista or the upper margin, deflects like a diaphragm, or displaces linearly in the mpulla. The only assumptions which are re lly required are that the cupula be somehow of supporting a pressure difference by ating forces which oppose its deflection. Following the notation of Van Egmond et al. (1949) the differential equation of motion of system is:

$$\Theta = -\Pi - \Delta + \alpha\Theta \qquad (7)$$

in which:

Π = viscous drag coefficient of the cupula/endolymph system, torque about the center of the canal duct per unit of angular velocity of the flow in the duct. [Viscous drag of endolymph in the canal duct, and possibly also viscous drag of the cupula (Steer 1967).]

= endolymph flow deflection angle in the duct.

Δ = torque coefficient on cupula/endolymph system about the center of the canal duct resulting from cupula motion per unit of angular motion of endolymph flow in the duct.

Behavioral responses give every indication that these dynamics are overdamped, and that the long time constant of the response Π/Δ is approximately 20 sec (see Young & Oman, 1969 Malcolm & Jones, 1970). It appears that the earlier estimates of Π/Δ from 8 to 10 sec in man based cupulograms or decay of sensation, were in error by failing to account for the effect of adaptation. Long term subjective and nystagmus responses show consistent evidence of adaptation involving a homeostatic mechanism of different relative strengths for the two response modalities respectively. Similarly the value of the short time constant (Θ/Π) appears to be 1/200th sec or less (Schmaltz, 1932, Steer 1967 Money et al. 1966, 1971), rather than 1/10–1/35 sec as determined from behavioral responses. It has become increasingly evident that behavioral response dynamics deviate significantly from the second order characteristics of the fluid dynamics because of intervening neurophysiological processes. The 0.005 sec time constant proposed by Money and others, is certainly unobservable on a behavioral basis. Studies by Benson (1970) and Nashner (1970) also suggest the presence of a rate-sensitive component with a time constant of 0.1 to 0.05 sec between cupula deflection and behavioral responses. Nerve recordings from semicircular first order afferents in the squirrel monkey by Goldberg & Fernández (1971) in response to rotational stimuli show adaptative and rate sensitive dynamics of a similar type to that seen in human behavioral responses. Rate-sensitive dynamics have also been observed in the nystagmic responses of the pike (Ten Kate 1969).

Accepting $\Pi/\Delta = 20$ sec, and $\Theta/\Pi = 0.005$ sec as estimates for the fluid dynamic time constants, one can determine that Δ should be equal to the product of the two time con-

stants of the system represented by equation (7) Hence·

$(\Delta \simeq 10\Theta = 2.4 \times 10^{-3}$ dyne cm/rad)

Now suppose one were to adopt the working hypothesis that the cupula rotates as a rigid body through an angle Ψ about a point at its base One can then relate this calculated value of Δ which is the torque on the endolymph ring per unit radian displacement in the duct, to events occurring in the ampulla. In particular by applying the continuity equation for flow between cross sections at the cupula and in the duct, one obtains

$$\frac{\Psi}{\zeta} = \frac{Ra^{3}}{B^{3}} \tag{8}$$

Now if K = the torque on the cupula, about *its base per unit cupula angular motion*

$$K = \frac{\Delta B^{4}}{a^{2}R^{2}} = 1.5 \times 10^{-3} \text{ dyne cm/rad} \tag{9}$$

and, from equation (5) one can determine that the cupula angle is:

$$\Psi = \frac{\prod B^{3}P}{K} = \frac{2\varrho\prod^{2}Fa^{2}R^{3}}{\Delta B^{3}}\alpha \tag{10}$$

accelerations of the 0 1 deg/sec² level as- ...iated with behavioral thresholds, the cupula ... ould deflect 0.177×10^{-4} ... s (0.001 deg). This corresponds to a d ... f the mid- point of the cupula of a ... y 0 01 mi- crons, *roughly three ord* ... *tude less than the width of the ha* ... *crista,* and a thirtieth the diamet ... ilium It is approximately the sa ... s the thickness of the unit mem ... air cells.

Another implication of th ... that the dynamic range cupu ... constrained to less than a third ... long term accelerations of less ... sec² *Actually almost all long* ... namic tests of canalicular response t ... acceleration are performed at ac

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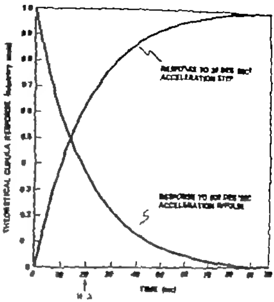

Fig 2 Theoretical cupula response to acceleration step and impulse.

levels considerably less than this. Acceleration levels considerably higher than 30 deg/sec² are commonly encountered in normal quick head motions, or in the cupulogram impulsive *stop. However the duration of these motions* is sufficiently short that large cupula deviations are never achieved. This is understandable ... is is well known, cupula displacement ... ately proportional to the time inte- ... *stimulus angular acceleratio* ... veral seconds after stim ... solution of the torsion p ... indicates that cupula de ... ments in angular a ... *deviations for step in* ... *by the factor of* 20. Hence it can ... e same peak cu ... in acceleratio ... *of 600 deg* ... conclude t ... locities ... to 90

The basic implication of the torsion pendulum model is that, for sinusoidal stimuli in the frequency range 0.1 to 10 radians sec, the cupula should act as a transducer of angular velocity. Tests in our laboratory indicate that in this frequency range human subjects can sustain self induced sinusoidal head motion up to only 600–700 degrees per second, and only at frequencies below 7–8 Hz. Hence, the linear model represented by equation (7) predicts that associated cupula deflection would always be less than a third of a degree, and midpoint displacements would be less than 3 microns.

It can be concluded, then, that although acceleration input amplitudes vary over a range of almost 10^4 above threshold, because of the nature of the frequency distribution of these acceleration stimuli, and the particular way in which the semicircular canal has evolved as a biological transducer, the dynamic range required of the cupula in the linear model appears to be only on the order of 10^2. Perhaps this provides a better match to the dynamic range characteristics of the afferent processes.

DISCUSSION

One obvious criticism of the foregoing argument is that the cupula may exhibit a torque-to-deflection saturation non-linearity at larger deflection amplitudes. Another is that perhaps, due to cupula viscous drag, the actual short time constant of the canal is less than the value of 0.005 seconds assumed here (Steer 1967). However, the effect of both of these errors is to increase the effective value of K which results in an even smaller, not larger value for the displacement threshold. Actually, however, the value of cupula stiffness calculated here seems not entirely unreasonable. The Young's Modulus of elasticity for a homogeneous cupula of height $2B$, thickness $B/2$, and stiffness coefficient K can be approximated as

$$E \approx \frac{16K}{B^3} \text{ dyne cm}^{-2} \tag{11}$$

This calculation does depend on assumptions associated with bending movement of inertia, and hence, on the assumed cupula thickness, so the results are only representative.

For $B = 0.06$ cm, equation (11) yields a value of 1.4×10^6 for E, which can be compared to values of 10^6 for rubber, and many for mucus found by Philippoff (1966) and 10^3 to 850×10^3 for gelatin found by Ferry (1967). It is consistent with values calculated by Ten Kate (1969) for the cupula of the pike, and for the cupula of the freestanding lateral line organ in *Necturus maculosus* (Oman, 1972).

It is important to note, that since the calculated range of cupula motion is very small for the actual range of the cupula, one cannot rule out the hypothesis that the cupula does not deflect about its base at the crista, as was assumed for this calculation, but rather generates equivalent torques on the endolymph due to lateral displacement as well. Some histological justification for this has recently been shown by Dohlman (1971). The volume displaced by a moving cupula is practically the same whether its midpoint traverses linearly or in an arc, for deflection angles up to about 10 degrees. In the former case, linear displacements at the level of the hair cell would be correspondingly larger. Obviously both alternatives have to be considered. Hence, the only conclusion justified from this analysis is that the dynamic range of the motion of the midpoint of the cupula, which displaces nearly identically under either hypothesis, is probably from ten millimicrons at threshold up to several microns for maximal self induced head motions, provided amplitude nonlinearities do not limit cupula displacements for the stronger stimuli.

It is interesting to note that the calculated threshold displacement in the semicircular canal is 10^4 larger than that calculated by Lawrence (1965) for displacement of the basilar membrane at the auditory threshold. However it should be noted that Lawrence's calculation is based on extrapolation of data taken by von Bekesy at 134 dB over threshold. ... ge of

displacement values calculated here for the cupula is generally consistent with the assumed dynamic range of the lateral line organs in fish and amphibians, as reported by Flock (1967). This discrepancy between auditory and vestibular/lateral line displacements is intriguing. While the calculated threshold in terms of displacements of the sensory structure are different by a factor of a million, the pressure thresholds for the semicircular canal and the human auditory system appear quite similar. The accepted standard for human auditory threshold at the tympanic membrane is 2×10^{4} dyne/cm², essentially the same value calculated for the semicircular canal.

CONCLUSIONS

The cupula of the human horizontal semicircular canal constitutes an important link in an extremely sensitive biological pressure transducer. One would expect it to be easily subject to trauma in research preparations or otologic surgery. Subjective behavioral thresholds to rotation are probably associated with cupula pressure differences of 10^{-4} dyne/cm². This small pressure is approximately equivalent to the acoustic threshold at the tympanic membrane. A pressure difference of 10^{-2} dyne/cm² robably required to produce nystagmus re nse to rotational or caloric stimuli. In the course of everyday life, peak pressure differences probably rarely exceed 10^{-2} dyne/cm². Hence, the application of even 10^{-4} cm of water pressure across the ampulla (0.1 dyne/cm²) would subject the cupula to a distinctly unphysiologic steady state pressure.

Calculations indicate that the dynamic range of motion of the midpoint of the cupula is from about 10 nm at threshold up to about 3 μm at the upper limit of self-induced sinusoidal head motions. The presence of a torque saturating characteristic in the cupula for large displacements could limit the upper end of the dynamic range to smaller values, however. Nonetheless, the dynamic range of motion calculated here is generally consistent with results obtained from the lateral line organs.

No conclusion is reached with respect to whether the cupula moves angularly or linearly or both, except that it should be noted that all modes are possible because of the small dynamic range of motions required. In any event, describing the cupula as a "swinging door" which normally makes gross displacements within the ampullary lumen is probably a misleading analogy.

ZUSAMMENFASSUNG

In den letzten Jahren wurde vielfach diskutiert, was auf die physiologischen Eigenschaften der Cupula beruhen. Es werden Ergebnisse und Berechnungen mitgeteilt, die darauf hinweisen, daß die Cupula einem biologischen Drucksensor entspricht, deren Schwelle von gleicher Größenordnung ist, wie die des Hörorgans. Danach wird die Cupula wahrscheinlich extrem leicht beschädigt, wenn bei dem Versuch Cupulabewegungen experimentell darzustellen, Druckgradienten wirksam werden, die weit jenseits des physiologisch-dynamischen Arbeitsbereiches der Cupula liegen. Nach den Berechnungen über den Umfang des dynamischen Arbeitsbereiches für Cupulabewegungen würde sich bei einer Beschleunigung von 0,1°/Sec², was etwa der vestibulären Schwelle entspricht, das Zentrum der Cupula um etwa 10 Millimikron bewegen. Beschleunigungen von 30°/Sec² oder plötzliche Geschwindigkeitsänderungen von 600°/Sec, welche typische Werte für maximale Willkürbewegungen des Kopfes darstellen, würden Cupulabewegungen von 3 Mikron bedingen. Nachdem die Cupulabewegungen so gering sind, können Bewegungskomponenten, *die parallel zur Crista und nicht auf einer* Kreisbahn um diese erfolgen, zwar nicht ausgeschlossen werden, wären aber aus denselben Gründen dynamisch nicht voneinander zu unterscheiden.

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displacement values calculated here for the cupula is generally consistent with the assumed dynamic range of the lateral line organs in fish and amphibians, as reported by Flock (1967) This discrepancy between auditory and vestibular/lateral line displacements is intriguing. While the calculated threshold in terms of displacements of the sensory structure are different by a factor of a million, the pressure thresholds for the semicircular canal and the human auditory system appear quite similar The accepted standard for human auditory threshold at the tympanic membrane is 2×10^{-4} dyne/cm² essentially the same value calculated for the semicircular canal.

CONCLUSIONS

The cupula of the human horizontal semicircular canal constitutes an important link in an extremely sensitive biological pressure transducer One would expect it to be easily subject to trauma in research preparations or otologic surgery Subjective behavioral thresholds to rotation are probably associated with cupula pressure differences of 10^{-4} dyne/cm² This small pressure is approximately equivalent to the acoustic threshold at the tympanic membrane A pressure difference of 10^{-3} dyne/cm² probably required to produce nystagmus response to rotational or caloric stimuli In the course of everyday life peak pressure differences probably rarely exceed 10^{-2} dyne/cm² Hence the application of even 10^{-4} cm of water pressure across the ampulla (0 1 dyne/cm²) would subject the cupula to a distinctly unphysiologic steady state pressure

Calculations indicate that the dynamic range of motion of the midpoint of the cupula is from about 10 nm at threshold up to about 3 μm at the upper limit of self-induced sinusoidal head motions. The presence of a torque saturating characteristic in the cupula for large displacements could limit the upper end of the dynamic range to smaller values, however Nonetheless, the dynamic range of motion calculated here is generally consistent with results obtained from the lateral line organs.

No conclusion is reached with respect to whether the cupula moves angularly or linearly or both except that it should be noted that all modes are possible, because of the small dynamic range of motions required. In any event, describing the cupula as a swinging door which normally makes gross displacements within the ampullary lumen is probably a misleading analogy

ZUSAMMENFASSUNG

In den letzten Jahren wurde vielfach diskutiert, was auf die physiologischen Eigenschaften der Cupula beruhen. Es werden Ergebnisse und Berechnungen mitgeteilt, die darauf hinweisen, daß die Cupula einem biologischen Drucksensor entspricht, dessen Schwelle von gleicher Größenordnung ist, wie die des Höhrorgans. Danach wird die Cupula wahrscheinlich extrem leicht beschädigt, wenn bei dem Versuch Cupulabewegungen experimentell darzustellen, Druckgradienten wirksam werden die weit jenseits des physiologisch-dynamischen Arbeitsbereiches der Cupula liegen. Nach den Berechnungen über den Umfang des dynamischen Arbeitsbereiches für Cupulabewegungen würde sich bei einer Beschleunigung von 0,1 /Sec² was etwa der vestibulären Schwelle entspricht, das Zentrum der Cupula um etwa 10 Millimikron bewegen. Beschleunigungen von 30°/Sec² oder plötzliche Geschwindigkeitsänderungen von 600°/Sec, welche typische Werte für maximale Willkürbewegungen des Kopfes darstellen, würden Cupulabewegungen von 3 Mikron bedingen. Nachdem die Cupulabewegungen so gering sind, können Bewegungskomponenten die parallel zur Crista und nicht auf einer Kreisbahn um diese erfolgen, zwar nicht ausgeschlossen werden, wären aber aus denselben Gründen dynamisch nicht voneinander zu unterscheiden.

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"NEW HORIZONS IN LARYNGOLOGY"

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We are assembled here today to honor one of the great otorhinolaryngologists of all time the Danish specialist Hans Wilhelm Meyer who is remembered for his discovery of the adenoid vegetations and their surgical eradication Why then was a *laryngologist* selected to speak on this special occasion? Perhaps the reason may be found in a review of Wilhelm Meyer's original article "On Adenoid Vegetations in the Nasopharyngeal Cavity" which was published in the Royal Medical and Chirurgical Society Transactions in the year 1870 (Meyer 1870).

In his opening remarks, Dr Meyer states: "Among the permanent defects of speech there is one that claims attention, not only on account of its rather common occurrence—at least with us in Denmark—but also on account of its frequent coincidence with a very marked *defect of hearing* In the first place then the voice is singularly wanting in resonance, and as the nasal consonants cannot be pronounced, the speech sounds short, stuffed, 'dead' as I would propose to call it, which is very uncharacteristic and unmistakable."

The author then relates his first case, a 20-year-old lady who continued to experience speech difficulties after a tonsillectomy She was given a course in training and pronunciation (voice therapy as we would call it today) with no better result. Dr Meyer then describes his dramatic voyage of exploration with the forefinger behind the soft palate up into the so-called *nasopharyngeal cavity* and his discovery of the soft masses which he termed "adenoid" vegetations. After their successful removal, Dr Meyer happily reported the result as most satisfactory: the voice became clear almost immediately and the patient was able to breathe freely through her nose. The author goes on to describe his experience in a great number of cases and adds, "Whenever the peculiar deadness of pronunciation occurred, these growths were invariably met with.

From this meticulous description it is apparent that Dr Meyer realized the importance of voice in our specialty: perhaps we should consider him one of our first successful phoniatrists because he restored the voice of his patients. *Could he join us today* I feel sure that he would approve our journey into the realm of voice to the new horizons of laryngology

Since the days of Dr Meyer many advances have taken place—social, economic, medical, and scientific. Our 20th century has been advertised as the century of the common man To reach this common man here, there and everywhere, our civilization relies on the mass media of communication—radio, motion pictures, and television all based on the impact of the human voice At the same time, our new methods of rapid transportation transfer from one continent to another our singers, our

Wilhelm Meyer Mode presented before the Dansk Oto-Laryngologisk Selskab in Copenhagen on November 6, 1971

actors, and our lecturers within the space of a few hours, and without an opportunity to ac climatize their vocal organ to the associated changes in climatic conditions and in the hu midity of the atmosphere. The noise of our urban society demands increasing vocal exer tions, while the pollution of air in our metropolitan centers injures the delicate lining of the respiratory structures, which are vital to the production of a pleasing voice. The emotional strains of our competitive industrial society also leave their mark upon our vocal organ for the voice has been acknowledged as the mirror of the soul.

The resulting clamor for medical attention encountered a profession which was ill-equipped for the demands of patients with different voice disorders, medico-legal problems, industrial disabilities, and psychosomatic ailments of the voice. Generations of medical students and laryngologists felt secure in the knowledge that all ills of the human voice could be evaluated with the aid of the trusty laryngeal mirror which, even in this age of inflation, may be purchased from every surgical supply house for less than the price of a necktie. As laryngologists, we had been led to believe that our surgical orbit revolved around the excision of tumors—a comforting state for everyone but the patient.

Only during the past decade has mounting pressure forced us to focus our attention on the human voice and its afflictions, and to adapt modern tools to the vocal ailments of our times. Fortunately for the laryngologist and his patient, these events have occurred during a period of unprecedented technological progress, and we have been privileged to take advantage of the developments in other medical and scientific disciplines. As a result of these efforts, the horizons of laryngology have expanded in all directions—from a better understanding of laryngeal physiology to new facilities for the diagnosis of voice problems and to newer techniques for their medical or surgical solution.

Thus, we have learned to think of phonation in terms of aerodynamic principles. We have discovered that a healthy voice depends upon the fine balance of physical forces between the *power* exerted by the pulmonary system and the *resistance* offered by the vocal cords at the level of the larynx. In this process we have developed an entirely new system of instrumentation for the early detection and diagnosis of laryngeal disease

At the same time our new knowledge of laryngeal physiology has permitted us to adapt new equipment and supplies for our surgical endeavors and to create new techniques for the improvement of laryngeal function and vocal pitch, intensity and quality This development of a new field of delicate physiologic surgery in turn presumes accurate, objective measurements of laryngeal function for diagnostic and comparative evaluations. Just as the otologic surgeon has to corroborate the success of his handiwork by appropriate audiologic studies, so the modern laryngologist should be willing to document his results with objective tests of laryngeal function and voice.

TECHNIQUES OF EXAMINATION

At the Institute of Laryngology and Voice Disorders in Los Angeles, we have attempted to combine the tried and true clinical techniques of laryngeal examination with more sophisticated, modern evaluations of the human voice (v Leden, 1971) The typical examination of a voice problem includes a detailed history a thorough evaluation of the ears, nose, and throat, indirect laryngoscopy with magnification, and the following three types of diagnostic function studies.

1 A careful examination of the vibratory pattern of the vocal cords
2. An aerodynamic evaluation of the laryngeal efficiency and pulmonary function, and
3 An acoustic analysis of the voice.

Radiologic studies, a direct laryngoscopic examination a photographic evaluation a psychologic interview and/or anc

tory studies are employed as indicated. The resulting data present a kaleidoscopic picture of the larynx in action: they have proved their usefulness for diagnostic and prognostic studies, medico-legal evaluations, and for comparative measures before and after surgery.

Both physician and patient benefit by our three-dimensional approach to a determination of laryngeal function. Alterations in the vibratory pattern are usually related to structural changes in the larynx; aerodynamic tests afford information about the efficiency of the vocal system, and the acoustic studies provide valuable data about the voice itself. These function studies are performed without any discomfort to the patient or for the examining physician; their sensitivity often permits the discovery of early changes in the larynx before the eye and ear of the examiner detect any physiologic or pathologic deviations.

Vibratory tests

The examination of the vibratory pattern may be conducted with the aid of an electronic stroboscope, electroglottography, or ultra-high speed photography.

For clinical evaluations, those three examinations supply essentially the same information about the vibratory movements of the two vocal cords. We prefer to utilize the electronic synchronstroboscope (v. Leden, 1961) or one of the newer glottographs (Loebell, 1968) for routine examinations, and to limit the costly and time-consuming photographic studies (v. Leden et al., 1966) to patients with abnormal vibratory oscillations. Since these examinations are well-known to this distinguished audience, I shall move on to the other investigations which we have developed.

Aerodynamic studies

Of special importance for our understanding of laryngeal physiology has been the adaptation of electronic equipment for aerodynamic studies. These objective tests are based on our current understanding of phonation as an aerodynamic phenomenon; measurements of selected aerodynamic factors should therefore provide a clue to the proficiency of the larynx in translating subglottic air-pressure into acoustic signals.

A schematic view demonstrates the major components of our aerodynamic system. A pneumotachograph is used for measurements of the air flow rate, air volume, and maximum phonation time. This equipment consists of a respiratory mask, a laminar flow register and a highly sensitive bi-directional differential gas pressure transducer. The voice signal is picked up by a condenser microphone which is located near the outlet of the pneumotachograph. The fundamental frequency of the voice is obtained from a contact microphone which is placed on the neck below the larynx. Additional components may be added for special studies as indicated, and all of the data are displayed on different channels of a polybeam recorder or on a cathode-ray oscilloscope (Ishiki & v. Leden, 1964).

These aerodynamic studies of laryngeal function require no special preparation and are readily performed with the average subject or patient. The simplicity of instructions and the lack of discomfort assure the cooperation of the patient, even in highly emotional singers or fearful children. A decrease in the mean air flow rate and in the air volume suggests abnormal tension of the laryngeal structures; by contrast, an increase in the mean air flow rate and in the air volume indicates a weakness of the neuromuscular component, with an abnormal escape of air. Fluctuations of the air flow rate present valuable information regarding functional voice disorders or psychosomatic problems (v. Leden, 1969). With the aid of pulmonary function studies, these data may be related to the balance of power and resistance at the level of the larynx.

The respiratory function of the patient is analysed with the aid of a respirometer or a plethysmograph. For clinical purposes, the mechanical function of the lung and thorax can be estimated from vital capacity studies. Together, these aerodynamic and respiratory

examinations provide the necessary data for an objective evaluation of laryngeal function in health and in disease. After extensive investigation, we have developed an objective clinical test which enables us to determine the quality of laryngeal function and the degree of impairment (v. Leden, 1968).

The clinical implications of this development are obvious. We are now able to determine the function of the larynx during phonation for an assessment of the physiologic status or for an evaluation of the therapeutic progress. Specific indications include pre- and postoperative comparisons, evaluations of a particular medical or phonatric treatment, determinations of injuries to the vocal structures, the detection of malingerers, and the solution of complex medico-legal problems (Yanagihara & v. Leden, 1967). During the radiotherapy of malignant lesions and during the prolonged observation of patients with various medical problems, these objective function studies have proved so sensitive that they usually signal physiologic improvement *before* the clinical examination of the patient confirms these findings (Werner-Kukuk et al., 1968).

Acoustic studies

Current investigations suggest that a comprehensive acoustic analysis may provide the earliest accurate information about pathologic changes in the larynx or voice disorders. Even minor variations in the vibratory pattern are accompanied by transient pressure changes across the glottis which are reflected acoustically in disturbances of the vocal signal.

We record the voices of all patients in a soundproof room with a high fidelity tape recorder and subject the resulting tape to a thorough acoustic analysis. *Frequency* determinations indicate the patient's habitual pitch and the vocal range which contracts during organic diseases. The *intensity* of the voice is related to vocal habits and voice disorders. A spectrographic analysis permits an accurate determination of the acoustic *quality* and objective measurements of hoarseness.

On the basis of extensive experiments, we have introduced an acoustic classification of the hoarse voice which is based on noise components in the main formants of vowel sounds, loss of acoustic energy in the harmonic components, and aperiodicity of the fundamental frequency (Yanagihara, 1967). Refinements in sound spectrography permit a three-dimensional analysis of hoarseness through the study of contour spectrograms, or "voice prints" (Iwata & v. Leden, 1970). For the detection of early laryngeal disease, we have found these sonagraphic measures far more sensitive than the human ear.

The application of electronic data processing and the use of *computers* provide a new dimension for an acoustic analysis of the human voice. Quantitative studies of short-term perturbations of the vocal pitch and concurrent modulations of the amplitude provide important information on pathologic changes in the vocal organ. For this evaluation, the voice is recorded with the aid of a contact microphone, and the minute differences in the pitch and/or amplitude of successive wave forms are measured and subjected to computer analysis. The simplicity and low cost of these acoustic determinations suggest an ideal screening medium for the early discovery of laryngeal disease (v. Leden & Koike, 1970).

SURGICAL PROCEDURES

With the development of these diagnostic criteria the science of laryngology has reached a level which encourages the development of surgical techniques for the restoration, preservation, and perfection of laryngeal function and voice production. In the United States, we have coined the term "phonosurgery" to encompass the different surgical procedures for the improvement of the voice. A survey of these techniques reveals a variety of approaches in different stages of development, including the adaptation of specialized equipment, the implantation of prosthetics, and the adoption of plastic and reconstructive techniques, such

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Aerodynamic studies

Of special importance for our understanding of laryngeal physiology has been the adaptation of electronic equipment for aerodynamic studies. These objective tests are based on our current understanding of phonation as an aerodynamic phenomenon measurements of selected aerodynamic factors should therefore provide a clue to the proficiency of the larynx in translating subglottic air pressure into acoustic signals.

A schematic view demonstrates the major components of our aerodynamic system. A pneumotachograph is used for measurements of the air flow rate air volume, and maximum phonation time This equipment consists of a respiratory mask, a laminar flow register and a highly sensitive bi-directional differential gas pressure transducer The voice signal is picked up by a condenser microphone which is located near the outlet of the pneumotachograph. The fundamental frequency of the voice is obtained from a contact microphone which is placed on the neck below the larynx. Additional components may be added for special studies as indicated, and all of the data are displayed on different channels of a polybeam recorder or on a cathode ray oscilloscope (Isshiki & v. Leden, 1964)

These aerodynamic studies of laryngeal function require no special preparation and are readily performed with the average subject or patient The simplicity of instructions and the lack of discomfort assure the cooperation of the patient, even in highly emotional singers or fearful children. A decrease in the mean air flow rate and in the air volume suggests abnormal tension of the laryngeal structures; by contrast, an increase in the mean air flow rate and in the air volume indicates a weakness of the neuromuscular component, with an abnormal escape of air Fluctuations of the air flow rate present valuable information regarding functional voice disorders or psychosomatic problems (v Leden, 1969). With the aid of pulmonary function studies, these data may be related to the balance of power and resistance at the level of the larynx.

The respiratory function of the patient is analysed with the aid of a respirometer or a plethysmograph. For clinical purposes, the mechanical function of the lung and thorax can be estimated from vital capacity studies. Together these aerodynamic and respiratory

mended a three-stage procedure. Recent modifications of this technique include a two stage procedure which includes the concurrent execution of Asai's first two maneuvers (Putney & Bagley 1970), and the use of skin flaps or esophageal flaps for the construction of the pseudo-larynx.

In a high percentage of cases, the resulting voice is remarkably good. When the patient closes the lower respiratory tracheostoma with his finger the air passes through the dermal tube which acts as a pseudolarynx the resulting vibrations give rise to sound waves which are amplified and transformed into speech. In return, the patient must contend with two inconveniences: the possible trickle of saliva into the tunnel, and the use of one hand for closure of the respiratory stoma during phonation. Since the introduction of the Asai laryngoplasty I have changed my technique for total laryngectomy to allow for a high tracheostoma and a secondary laryngoplasty if the patient is unable to master a satisfactory esophageal voice.

Reconstructive procedures

Other procedures are indicated occasionally for the improvement of voice After a laryngofissure with a cordectomy a substitute vocal fold may be constructed from a mucosal or dermal flap. Septal cartilage may be implanted into the vocal cord via the suspension laryngoscope with microsurgical techniques. Portions of the thyroid cartilage and of the extrinsic laryngeal muscles may be transposed to improve the voice after a partial resection of the larynx.

All laryngologists await the day when an entire larynx can be transplanted as a functional organ. While this difficult feat was accomplished in a single case by Kluyskens at the University of Ghent three years ago (Kluyskens et al., 1969), many difficulties must be overcome before laryngeal transplantation becomes an accepted procedure. Even if immunologic acceptance of the transplanted larynx can be assured, ultimate success awaits a breakthrough in the reconstruction of the nerve supply in the transplanted organ.

CONCLUSION

Recent advances in laryngology have created new hope for man's chief instrument of communication—his voice. While the tribulations of our modern environment create more and more stress for the human larynx, medical science labors to protect, restore, and improve the human voice.

During the past decade, laryngeal research has produced diagnostic facilities for the objective measurement of laryngeal function and for the qualitative determination of the voice. The resulting data permit objective evaluations of functional disorders, earlier detection of laryngeal disease, and an impartial comparison of various surgical techniques and of conflicting therapeutic results.

Surgical pioneers in different countries have developed a series of new surgical techniques for the improvement of vocal function. These procedures include the perfection of new equipment, the utilization of various implants, and the development of new plastic and reconstructive procedures.

On the basis of these recent achievements, I visualize a new dawn on the horizon of laryngology when the laryngologist can assure every patient his full vocal potential.

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VIBRATORY PATTERN OF THE VOCAL CORD IN UNILATERAL PARALYSIS OF THE CRICOTHYROID MUSCLE

An Experimental Study

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Abstract. The effect of unilateral paralysis of the cricothyroid muscle on the vocal cord position and length and vibratory pattern was investigated in dogs through the use of normal and high speed cameras. After unilateral section of the external branch of the superior laryngeal nerve, the arytenoid on the active side adducts across the midline toward the paralytic side. Unilateral contraction of the cricothyroid muscle elongates both vocal cords conspicuously though more on the active side than on the inactive side. In the case of unilateral contraction of the cricothyroid muscle, the two vocal cords vibrate at the same frequency and the vocal cord on the side of active cricothyroid muscle always precedes the opposite cord in vibratory cycle

On stroboscopic examination of the pathologic larynx we notice, not infrequently an asymmetrical vibration of the vocal cord, especially in amplitude. A tumour or infiltration, if noted on or in one vocal cord, would well account for reduced amplitude of vibration of that cord. If there is no apparent difference in mass or shape between the two cords, one of the possible explanations for the amplitude difference would be tension imbalance between the two vocal cords.

In normal phonation, the amplitude of vibration of the vocal cord is generally greater at low pitch than at falsetto. From this fact, we may deduce that the vocal cord vibrating with smaller amplitude would be tenser than the opposite cord. Furthermore, can we generally deduce that the cricothyroid muscle (and vocal muscle) on the side of smaller amplitude would predominate over the opposite cricothyroid muscle (contralateral paresis of the cricothyroid muscle)?

The above presumptions appear clinically very important in connection with the diagnosis of unilateral paralysis of the cricothyroid muscle. Such hypothetical interpretation of the stroboscopic finding as the above may turn out to be related to the treatment of so-called functional dysphonia in which the asymmetrical amplitude of vibration of the vocal cord is often observed.

The vibratory pattern of the human vocal cord, normal and pathologic has been extensively investigated by many previous researchers (Kirikae 1943 Smith, 1954 Timcke, 1956 Timcke et al., 1958 1959 Moore & v Leden, 1958 Berendes & Luchsinger 1958 Dunker & Schlosshauer 1958 Luchsinger & Arnold, 1959 Jeschek, 1959 v Leden et al., 1960· Rubin & Le Cover 1960· Schönhärl, 1960· v Leden & Moore, 1961 Hiroto, 1966) and much knowledge has been obtained on the mechanism of vocal cord vibration.

In clinical cases, however many factors such as changes in mass, tension and shape are usually involved simultaneously Moreover unilateral paralysis of the cricothyroid muscle is

regarded as a rare clinical entity and, due to rather insignificant or unspecific symptoms and signs, the diagnosis does not always seem so definite, although the diagnostic procedures were well summarized recently by Arnold (1961) and Luchsinger (1965)

As a first step, experimental study is needed to reveal the effect of tension imbalance on the *vibratory pattern of the vocal cord.* So far as the available literature is concerned, no investigations have been made on the vibratory pattern of the vocal cord under asymmetrical contraction of the cricothyroid muscles produced experimentally

EXPERIMENTAL PROCEDURE

Utilizing 11 adult dogs, laryngeal appearance and vibratory pattern of the vocal cord during phonation were photographed for analysis under varied conditions imposed on the cricothyroid muscle

(A) *Preparation of the dog*

The dogs were anesthesized with Thiamylal Natrium 15 mg/kg i.p. For better visualization and photography supraglottal laryngectomy was performed. The external branch of the superior laryngeal nerve was identified and prepared long enough for further experimental ...cedure. The animal was fixed recumbent on table carefully so as to avoid any twisting of the larynx.

(B) *Experimental conditions*

The effect of contraction or paralysis of the cricothyroid muscle on the vibratory pattern of the vocal cord was examined under the following five experimental conditions. They are: 1 unilateral section of the external branch of the superior laryngeal nerve 2, bilateral section of the nerve 3 electric stimulation with 50 Hz, 5 V and 5 msec duration rectangular wave on unilateral cricothyroid muscle after bilateral section of the nerves 4 in the extirpated larynx, contraction of unilateral cricothyroid muscle was simulated by mechanical approximation of the cricoid and thyroid cartilages on one side 5 stretching of the unilateral vocal cord by direct pull of the arytenoid cartilage posteriorly

In each dog, the vibratory pattern of the vocal cord without imposing any of the above experimental conditions was photographed first as a normal control. Voice production was elicited mostly by pain stimuli but on occasion (two cases) when the above stimuli failed to evoke vocalization due to too deep anesthesia, voice was produced by utilizing the Hering-Breuer's reflex.[1]

(C) *Photographing*

Laryngeal appearance such as the position and axis of the glottis and the vocal cord length was analysed by means of motion film taken at a speed 24 frames/sec. For this purpose, subglottal air flow was not provided in the tracheotomized or extirpated cases.

For analysis of the vibratory pattern of the vocal cord, a high speed motion film was taken during phonation (Hycam Model K2001 by Red Lake Lab Inc., 4 000–6 000 frames/sec). Timing marks were plotted on one side of the film each 1 msec. The films were studied through frequent projection, and further detailed frame-by-frame analyses were made on selected films by film analyzer (Nac Motion analyzer Model 16-S).

RESULTS

(A) *Laryngeal picture*

Displacement and elongation of the vocal cord induced by unilateral contraction or paralysis of the cricothyroid muscle were studied on 9 dogs. Fig. 1 represents the laryngeal picture in case of section of the external branch of the superior laryngeal nerve on the left. This picture for unilateral nerve section was essentially the same as that obtained for contralateral stimulation of the cricothyroid muscle after bilateral nerve section. The arytenoid on the active side adducted across the midline toward

[1] Tracheotomy was performed and a tube was connected airtight with the stoma. Blowing through the tube into the trachea gave rise to closure of the glottis and sustained voice production.

Fig. 1 The laryngeal picture in case of section of the external branch of the superior laryngeal nerve on the left.

the paralytic side. The thyroid cartilage also rotated so that the active side of the thyroid cartilage moved forward and the paralytic side backward. Consequently the vocal cord on the cricothyroid-active side elongated more than the paralytic side. More specifically in cases where measurements were made, the vocal cords of 12 mm (average length) elongated 3 mm on the active side and 2 mm on the paralytic side. Although the degree of rotation of the glottal axis or of the thyroid cartilage was variable with the cases (3.5–17.0 degree), the general picture was quite consistent among the different cases in identical conditions. In none of the cases did the vocal cords become wavy or serrated in appearance.

(B) *Vibratory pattern of the vocal cord*

The vibratory patterns of the vocal cord in cases of unilateral section of the external branch of the superior laryngeal nerve were essentially identical with those in cases of contralateral stimulation of the cricothyroid muscle after bilateral nerve section.

1 The two vocal cords vibrated exactly at the same frequency The vibrations were periodic and no sudden changes of vibration such as fluttering movement were observed (Fig. 2 *A B C*)

2. Phase difference was noted in the vibration of the two cords. The vocal cord on the side of active cricothyroid muscle started opening and closing earlier than that on the paralytic side In other words, lag in phase was noted on the paralytic side (Fig. 2 *A B C* and Fig. 3). The above findings as to the frequency and phase were consistently noted in all of the 9 dogs.

3 As to the amplitude of vibration, however the findings were rather diversified. In 4 of 9

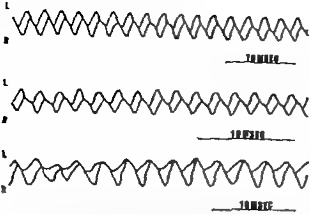

Fig 2. The vibratory pattern of the vocal cord. (*A*) After section of the external branch of the superior laryngeal nerve on the left. (*B*) Stimulation of the cricothyroid muscle on the right after bilateral nerve section. (*C*) After section of the external branch of the superior laryngeal nerve on the left.

cases, no essential difference in amplitude between the two cords was noted (Fig. 2 *A* *B*) However in 5 cases, the amplitude of vibration on the cricothyroid-active side was slightly greater than on the non-active side (Fig. 2 *C*)

On the extirpated larynx, where the cricothyroid distance was mechanically approximated on one side, there were no differences in the frequency between the two vocal cords. The phase difference as mentioned above was also noted. The amplitude of vibration was greater on the active (cricothyroid-approximated) side than the non-active side (Fig. 4 *A*) When one vocal cord of the extirpated larynx was strongly stretched by direct pull of the arytenoid posteriorly the tense vocal cord vibrated with much less amplitude (Fig. 4 *B*)

DISCUSSION

Diagnosis of unilateral paralysis of the cricothyroid muscle is usually made on the basis of laryngoscopic, vocal, stroboscopic and radio-

Fig 3 The vibratory pattern of the vocal cord after section of the external branch of the superior laryngeal nerve on the right. Lag in phase is noted on the paralytic side.

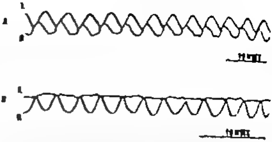

Fig 4 The vibratory pattern of the vocal cord. (*A*) In the extirpated larynx, the cricothyroid distance was mechanically approximated on the left. (*B*) In the extirpated larynx, the left vocal cord was stretched by direct pull of the arytenoid cartilage posteriorly

logic findings, as proposed by Arnold (1961). Discussion on the present findings is made along this line

1) *Laryngeal picture*

As an important sign of unilateral paralysis of the cricothyroid muscle, oblique glottis or "deviation of the posterior commissure to the affected side" has been pointed out experimentally as well as clinically by many previous authors (Riegel, 1870; Neumayer 1896 Mygind, 1906 Stupka, 1924, Luchsinger 1940, 1942, Döhne, 1941 Arnold, 1948 Gregg, 1956 Arnold, 1961 Faaborg-Andersen & Jensen, 1963) As to this point, the present finding is nothing new but essentially the same as the above view which was already well documented.

Heinemann (1969) and Baldus (1963) reported many cases of laryngeal asymmetry of various types and causes.

Differential diagnosis among various laryngeal asymmetries often seems difficult and remains to be investigated in order to make diagnosis of unilateral paralysis of the cricothyroid muscle definite.

Many of the previous studies emphasize lack of vocal cord tension on the side of inactive cricothyroid muscle, expressed as flaccid vocal cord moving up and down floppingly in the respiratory air flow (Burow 1877 MacKenzie, 1880 Mygind, 1906 Arnold, 1961) or wavy appearance of the vocal cord (Lublinski, 1901 Mygind, 1906)

The present experiment on dog clearly demonstrates that the vocal cord on the side of the inactivated cricothyroid muscle is stretched remarkably (2 mm elongation for 12 mm vocal cord) by the contraction of the opposite cricothyroid muscle, though less than the active side (3 mm) It is a matter of course that the result obtained in dog cannot be applied to humans without modification. The dog larynx differs from the human larynx in number, relative size and position of the muscle and cartilage and particularly innervation of the transverse arytenoid muscle (Vogel 1952) However judging from the anatomical structure of the thyroid and cricoid cartilages in dog and human, it seems reasonable to presume a similar effect in human too though it would be different in degree. The preconceived idea of "side-independence" in controlling the vocal cord tension, which made frequent appearance in previous literatures, should be corrected.

2) *Vibratory pattern of the vocal cord*

(*a*) Frequency In the present experiment, contraction of the unilateral cricothyroid muscle resulted in asymmetrical elongation of the vocal cords. Different tension between both cords is therefore presumed. Under this condition, both the vocal cords always vibrated synchronously It would be under quite a critical condition if different tension of the two vocal cords produces vibration at two different frequencies, so far as the glottis is completely closed.

(*b*) Phase: The vocal cord on the side of active cricothyroid muscle always preceded the mate in the vibratory cycle. Tension imbalance alone cannot explain the consistent finding of phase difference. The explanation requires further research.

(*c*) Amplitude: The experiment on the extirpated larynx confirmed the principle that the tenser vocal cord vibrates with smaller amplitude In case of unilateral contraction of the cricothyroid muscle, however the amplitude of vibration on the active side was, contrary to our expectation, not smaller than the inactive (less tense) side. The factor other than tension, that is shift of the glottal axis, is also involved in this case, and consequent imbalance of the area on which the subglottal air pressure is applied would also have to be taken into consideration for explaining the above phenomena as to the phase and amplitude.

As to the vibratory pattern of the vocal cord in unilateral paralysis of the cricothyroid muscle Döhne (1941) described the stroboscopic finding as regular dashing-through (durchschlagend) movement which is easily switched to clear flutter In contrast to Döhne's finding, Luchsinger (1942) reported distinct dashing-against-each-other (gegenschlagen) movement of the vocal cords, which also shifts to flutter as Döhne described. Arnold (1961) summarized the stroboscopic finding as (*a*) arrhythmia or disturbed symmetry between the two cords (*b*) rapid loss of vibrating regularity and appearance of an irregular flutter as a sign of different tension in the two cords, or (*c*) replacement of normal vibrations by pathologic vertical movements of the affected cord, indicating its flaccidity and weakness. The stroboscopic finding which Döhne described as "durchschlagende Bewegung" may be interpreted as phase shift of vibration between the two cords.

3) *Voice*

Most of the previous reports are in agreement that the voice in unilateral paralysis of the cricothyroid muscle is characterized by monotonous and low pitch and inability to sing a high tone (Mygind, 1906 Luchsinger 1942 Arnold, 1961) and difficulty of after singing (simulation) (Luchsinger 1942 Arnold, 1961) Whether the voice is hoarse or not is controversial. Mygind (1906) mentioned that the voice (human) was not hoarse while Némai (1937) Lemere (1933) (dog) described the voice as hoarse. In human, Moran & Castro (1951) reported that purposeful traumatization of unilateral external branch of the superior laryngeal nerve in four cases of thyroid-

ectomy resulted in hoarse and monotonous voice which was noticeable for about a week. Mygind (1906) maintained that the reported cases of aphonia in case of unilateral paralysis of the cricothyroid muscle would be either due to misdiagnosis or due to other combined nerve paralysis.

In the present experiment, unilateral inactivation of the cricothyroid muscle resulted in marked lowering of pitch but the voice was not hoarse in any case. Analysis of the voice revealed periodicity of vibration, confirming that the voice is not hoarse.

Whether the voice becomes hoarse or not depends not only on the glottal condition but also on the subglottal air flow especially so when the vocal cord is rather lax, as already reported by one of the authors (Isshiki, 1971) The voice can be hoarse if disproportionately strong air flow is applied to the lax vocal cords. Besides, the clinical cases of unilateral paralysis of the cricothyroid muscle previously reported are mostly after thyroidectomy Such being the case, the effect of postoperative edema or inflammation of the vocal cord on the voice cannot be overlooked

In summary there are many controversial points in the finding previously reported of unilateral paralysis of the cricothyroid muscle. The discrepancies may be attributable to the following factors. 1 the different methods employed for examination, high speed camera or stroboscope for instance 2, difference between dog and human (the cricothyroid muscle appears relatively massive in dog as compared with that in human) 3 in clinical cases many factors are simultaneously involved and there is some uncertainty in the diagnosis due to rather indistinct symptoms and 4 other factors related with voice production such as subglottal pressure

Faaborg-Andersen & Jensen (1963) maintained that the isolated paralysis of the superior laryngeal nerve is not so rare as previously believed, reporting five cases they encountered in a year They based the diagnosis on the laryngoscopic picture (the oblique glottis) and the electromyographic findings. Luchsinger (1965) also emphasized the usefulness of electromyography in the diagnosis of the isolated paralysis of the cricothyroid muscle, on the basis of his three clinical cases. Clinical cases should be reevaluated in the light of the experimental results.

Turning back to the question raised in the introduction, we cannot simply regard amplitude difference of vibration between the two cords as a sign of asymmetrical activity of the cricothyroid muscle. In case of such stroboscopic finding, rheological properties of the vocal cord, change of elasticity due to scar tissue for instance, should also be taken into consideration.

CONCLUSION

The effect of unilateral paralysis of the cricothyroid muscle on the vocal cord position and length and the vibratory pattern was investigated in dogs by use of normal and high speed cameras.

Within the limits of experimental subjects and other conditions, the following conclusions were drawn.

1) Unilateral contraction of the cricothyroid muscle gives rise to deviation of the posterior commissure of the glottis to the inactivated side.

2) Unilateral contraction of the muscle elongates both vocal cords conspicuously though more on the active side than on the inactive side.

3) In case of unilateral contraction of the cricothyroid muscle, the two vocal cords vibrate at the same frequency The vocal cord on the side of active cricothyroid muscle always precedes the opposite cord in vibratory cycle. The amplitude of vibration on the active side is not significantly different from or rather greater than the inactive side.

ZUSAMMENFASSUNG

Die Auswirkung der einseitigen Lähmung des M. cricothyreoideus auf die Lage, Länge und Schwingung der Stimmbänder wurde bei Hunden durch den Gebrauch von normalen und ultraschnellen Kameras erforscht. Nach einseitiger Durchschneidung des R. externus N.

laryngeus superior geht der Aryknorpel über die Mittellinie zu der gelähmten Seite über Einseitige Zusammenziehung des M. crico-thyreoideus verlängert beide Stimmbänder auffallend, obgleich mehr an der tätigen Seite als an der gelähmten Seite. Im Falle der einseitigen Zusammenziehung des M. crico-thyreoideus vibrieren beide Stimmbänder in der gleichen Frequenz und das Stimmband an der Seite der tätigen M. crico-thyreoideus geht immer dem gegenüber liegenden Stimmband im vibrierenden Zyklus voraus

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GENERAL ANESTHESIA FOR MICROLARYNGOSCOPY USING SMALL BORE ENDOTRACHEAL TUBES

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Abstract Po_2, Pco_2 and pH were measured in two groups of patients during microlaryngoscopy performed under general anesthesia with small-bore tubes and controlled manual ventilation. The first group (4 patients) being intubated with an ordinary French gauge 18 Rüsch tube developed a CO_2 accumulation, whereas oxygenation was sufficient. In the second group (8 patients) a "Pollard-type" of tube was used, of small bore (I.D. 4 mm) in the distal part, wider (I.D. 6 mm) in the proximal part. This tube *fulfilled* the anesthesiological demand for adequate ventilation and the surgical need for free access and exposure of larynx.

The combined use of suspension laryngoscope and operating microscope as introduced by Kleinsasser (1965) provides excellent exposure the larynx and the possibility of performing geal microsurgery This procedure calls for special demands on the anesthesiological technique, as both absolute immobility of the surgical field, necessitated by the use of microscope as well as adequate ventilation during the relatively prolonged procedures can only be obtained safely with the patient completely relaxed and intubated.

For intubation armoured cuffed tubes have been used (Westhues, 1966; Weigard, 1970) but a tube size fitting the surgical purpose will in most cases be considered by the anesthesiologist as too small for adequate ventilation The problem was solved by Pollard (1968) who designed a tube, small bore in the distal part (internal diameter = I.D. 5–7 mm), wider (10 mm) in the proximal part. Ventilation through this tube is adequate using a 5 mm tube for women and a 6 or 7 mm tube for men. Ventilation by a positive-negative phase respirator as used in Kleinsasser's cases (Westhues, 1966) is not necessary as the residual tracheal pressure during expiration did not exceed 3 mmHg, nor did it depress the circulation in any patient manually ventilated by Pollard (1968).

To provide optimal working conditions for the surgeon our aim has been to find the smallest size of endotracheal tube which ensures adequate CO_2 elimination and oxygenation in the average anesthetized adult when ventilation is controlled manually in an ordinary circle system.

MATERIAL AND METHOD

Twelve patients aged 42 to 68 years (mean 55 years) average weight 79 8 kg (range 51 7–93 kg) and average height 170 cm (range 153–182 cm) were studied during microlaryngoscopy

Premedication consisted of pethidin-atropine given intramuscularly 1 hour before surgery. Anesthesia was induced with [illegible]lbomal-sodium (Narcodorm®) followed by halothane and N_2O/O_2 (6 + 3 litres) by mask for 3 min. After this time intubation was performed facilitated by suxamethonium. The armoured endotracheal tube was introduced by help of a

Table I *Blood gases and pH in patients intubated with a French gauge 18 tube*

Patient no.	Before intubation	After intubation 5 min	15 min	25 min
P_{CO_2} (mmHg)				
1	55	57	59	59
2	56	68	69	69
3	49	63	61	58
4	40	59	52	65
Mean	50	61.8	60.2	6_.8
S.E.	3.7	2.4	5.8	2.6
P_{O_2} (mmHg)				
1	155	200	190	195
2	111	90	185	170
3	190	133	185	195
4		158	200	230
Mean	152	145	190	198
S.E.	23.4	23.0	3.5	12.3
pH				
1	7.29	7.28	7.26	7.28
2	7.29	7.22	7.21	7.19
3	7.27	7.23	7.24	7.25
4		7.23	7.20	7.19
Mean	7.28	7.24	7.23	7.23
S.E.	0.007	0.014	0.014	0.023

S.E. indicates one standard error
No value as blood sample was clotted.

stylet. Anesthesia was continued with halothane and N_2O/O_2 (2.5 + 2.5 1) and relaxation achieved by a continuous infusion of suxamethonium. Ventilation was manually controlled in a circle system with a respiratory frequence of 14–18/minute peak inflation pressures were monitored with a Tyco® manometer

Arterial blood samples were drawn from an indwelling catheter in a radial artery immediately after induction and 5 15 and 25 min after intubation (patients 1–4) in patients 5–12 a sample too was drawn before induction. The samples were drawn in heparinized syringes, immediately cooled on ice and analysed in a Radiometer® electrode-assembly for P_{O_2}, P_{CO_2} and pH.

Patients 1–4 were intubated with an ordinary armoured French gauge 18 Rüsch® tube (I.D. 3 mm, length 25 cm) furnished with a 5 cm long cuff. A self-constructed "Pollard-type" tube was used in patients 5–12, the distal part being 14 cm, French gauge 18 (I.D., 4 mm) the proximal part 16 cm, French gauge 24 (I.D., 6 mm) the two parts were glued together and mounted with a 5 cm cuff The latter tubes (Flotex®) are only available in pediatric length (the reason why a Rüsch tube was used in the first part of the experiment), but has a thinner wall than the Rüsch tube so that 1 mm is gained in internal diameter at the same external diameter

RESULT

In patients 1–4 (Table I) P_{CO_2} increased to about 60 mmHg within the first 5 min of anesthesia and remained at this level in spite of inflation pressures of 40–60 mmHg The pH-values indicated an increasing uncompensated respiratory acidosis, while oxygenation was sufficient.

The results obtained with the self-constructed Pollard tube are listed in Table II. During ventilation by mask, P_{CO_2} increased and was elevated for the first 5 min after intubation but ventilation through this tube was sufficient to bring P_{CO_2} down to initial values within 15 min and to normalize pH. All P_O values were within safe levels. Patients 5–12 were ventilated with inflation pressures of 20–35 mmHg Pulse and blood pressure remained stable in the two groups of patients, which are well comparable as to age weight and height.

DISCUSSION

The self-constructed Pollard tube which has a smaller diameter than the original Pollard tubes, will provide adequate respiration on manual ventilation even in well-built male patients, whereas the overall 4 mm tube is too small to ensure adequate CO_2-elimination.

The Pollard tube with its narrow intralaryngeal and intrapharyngeal section gives excellent exposure and free access to any part

Table II. *Blood gases and pH in patients intubated with French gauge 18 "Pollard" tube*

Patient no	Before premed.	Before intubation	After intubation 5 min	15 min	25 min
P_{CO_2} (mmHg)					
5	44	60	40	45	37
6	43	50	48	33	31
7	48	74	68	52	59
8	43	47	52	45	45
9	45	49	52	40	44
10	(58)	47	53	50	45
11	43	5[illegible]	56	40	37
12	50	52	64	43	47
Mean	45.1	53.9	54.1	43.5	43.1
S.E.	1.0	3.2	3.1	2.1	3.0
P_{O_2} (mmHg)					
5	75	75	240	198	200
6	95	200	255	270	310
7	83	59[a]	200	220	205
8	80	225	116	139	180
9	80	235	205	210	200
10	(38)	158	195	215	200
11	82	138	200	255	260
12	83	73	145	285	280
Mean	82.6	145.4	194.5	224	229.4
S.E.	2.3	25.1	12.6	16.0	16.7
pH					
5	7.37	7.23	7.31	7.31	7.39
6	7.36	7.29	7.32	7.24	7.46
7	7.32	7.22	7.24	7.28	7.27
8	7.33	7.31	7.28	7.31	7.29
9	7.34	7.32	7.30	7.36	7.33
10	(7.30)	7.32	7.29	7.33	7.34
11	7.32	7.29	7.23	7.32	7.34
12	7.33	7.31	7.28	7.37	7.36
Mean	7.34	7.29	7.28	7.32	7.34
S.E.	0.008	0.014	0.011	0.015	0.021

S.E. indicates one standard error.
[a] Low P_{O_2} and high P_{CO_2} due to laryngospasm.
( ) Venous sample, excluded from the series.

of the larynx as its position can be shifted as needed.

The use of general anesthesia with endotracheal tube offers several advantages over other methods used for laryngoscopy such as apneic oxygenation (Woodman, 1961) artificial ventilation by cuirass respirator (Knudsen et al. 1958 Hauser & Brown, 1967), inhalation anesthesia with spontaneous ventilation, by some combined with field block (DeSanto & Carney 1970) and ventilation via commissure laryngoscope (Bløndal et al. 1964)

The presence of a cuffed endotracheal tube will prevent blood and debris from larynx from being aspirated into the lungs and allows liberal use of suction in larynx without the risk of reducing blood oxygen tension (Boutros, 1970) Adequate depth of anesthesia can be established and maintained and since the ventilation is also adequate, any time factor for examination and surgery is eliminated. Suction through the thin tube is difficult to perform and must be done with stiff catheters.

ZUSAMMENFASSUNG

P_{O_2}, P_{CO_2} und pH wurden in zwei Patientengruppen während Mikrolaryngoskopie unter Vollnarkose mit englumigen Spiraltuben und kontrollierter manueller Beatmung gemessen. Die erste Gruppe (4 Patienten), die mit einem allgemeinen Rüsch Tubus (French gauge 18) intubiert war, entwickelte Kohlensäureanhäufung, während die Sauerstoffspannung zufrieden war. In der anderen Gruppe (8 Patienten) wendete man einen Tubus von „Pollard-typ" an. Dieser Tubus hatte in dem distalen Teil einen kleinen Durchmesser (innerer Durchmesser 4 mm), und einen größeren (6 mm) in dem proximalen Teil, und stellte die anästhesiologische Forderungen für adekvate Beatmung und den chirurgischen Bedarf für freien Zugang zu Larynx und optimale Sicht für den laryngoskopischen Eingriff zufrieden.

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LIP MUSCLE FUNCTION IN PARKINSONIAN DYSARTHRIA

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Abstract The articulatory EMG activity of lip muscles was investigated in patients with Parkinsonism and dysarthria and compared with normal-speakers. Furthermore, the effect of L-Dopa treatment on the dysarthric EMG activity was evaluated. Although articulatory ability improved in the experimental situation, it was possible to recognize reproducible abnormalities of the EMG pattern common to all patients. The resting activity between utterances was markedly increased and often progressed to a sustained hypertonic background activity particularly in M. lev lab and M. dep. lab., as a sign of an exaggerated speech posture during the utterance. The functional organization of the lip muscles into two antagonistic groups for contrasting speech gesture movements was impaired. There were no signs of reciprocal inhibition. There was an obvious relationship between this disturbed activity pattern and the misarticulation of labial stop consonants. Furthermore, a longer anticipa- period and a lack of context dependence of the IG activity were often observed. L-Dopa medication was followed by a reduction of background activity and a reestablishment of reciprocal activation. These findings are discussed in relation to available data on limb muscle function in Parkinsonism.

Speech disorder is common in Parkinsonism and may even be a predominant symptom Although speech pathologists have been concerned with the linguistic and phonetic aspects of Parkinsonian speech for many years (for references see Wode, 1970) the descriptions are mainly based on acoustic observations. A thorough analysis of the disturbed control of speech gesture movements can hardly be achieved acoustically however Therefore other methods have been tried and some data are available on the use of EMG with surface electrodes for the study of articulatory lip muscle activity in Parkinsonian dysarthria (Krival, 1965)

In earlier studies (Leanderson et al., 1971 *a*) an EMG method with needle electrodes was developed for analysing normal activity patterns during labial articulation. This method is employed here to obtain a description of the EMG patterns of lip muscles in Parkinsonian patients with a view to analysing labial dysarthria. The findings are then used to evaluate the effect of L Dopa medication on the disturbed labial articulatory function in Parkinsonian patients. Some of the results have been presented in preliminary reports (Persson et al., 1969 Leanderson et al., 1970, 1971 *b*).

METHODS

The present study comprised 12 patients (mean age 56 8 years) with Parkinsonism and dysarthria (mean duration of the disease 7- years) All of them displayed rigidity and *hypokinesia* 5 had resting tremor 6 had undergone stereotaxic surgery on one side and 6 were non-operated 3 were investigated several times over a period of 2 years 5 w studied before and after L-Dopa treatment.

The articulatory activity of the labial musculature was recorded polygraphically with the

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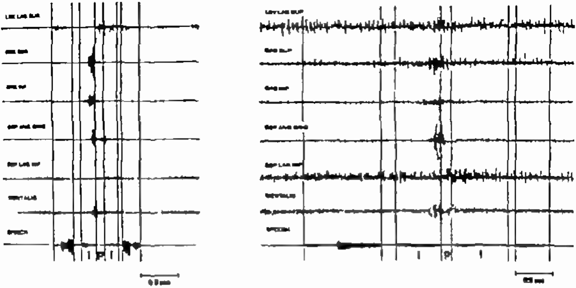


Fig 1 EMG recordings of lip muscle activity for the VCV combination [ipi] in a normal-speaker (left) and a patient (right) with Parkinsonism and dysarthria. Note in the recording from the patient the increased resting and background activity partly obscuring the articulatory activity

concentric needle electrodes simultaneously with the speech signal. The following 6 muscles in one half of the face were investigated. M. lev lab sup., M orb oris sup., M. orb. oris inf M. dep lab oris, M. dep ang oris and M. mentalis. The experimental procedure has been described in detail in an earlier publication (Leanderson et al., 1971 *a*) In the operated patients the non-operated side, which showed typical Parkinsonian symptoms, was investigated and in the non-operated patients the side of the face was chosen ipsilateral to the most rigid and hypokinetic half of the body The patients were asked to read the phonetic material twice before three consecutive recordings were made Misreadings were excluded and corrected in order to obtain complete recordings from each patient.

RESULTS

The spontaneous connected speech of each of the patients exhibited many of the acoustic features characteristic of Parkinsonian speech disorder (cf Grewel, 1957 Darley et al., 1968). In the experimental situation, however the articulatory ability in particular improved and all patients mastered the test readings, providing satisfactory recordings for an analysis of the articulatory EMG in Parkinsonian patients as compared with a normal-speaking group (Leanderson & Lindblom, 1972).

In keeping with earlier findings in normal-speakers, the articulatory EMG pattern of the patients displayed good reproducibility in sequential readings of the same utterance and presented individually recognizable features. Even with these individual variations, it was possible to observe EMG characteristics common to all the patients. The results from operated patients did not differ from those from non-operated patients.

Resting and background activity

Fig. 1 presents for comparison EMG recordings from the lip muscles for the VCV combination [ipi] in a normal-speaker (left) and a Parkinsonian patient with dysarthria (right). In the normal-speakers a very slight resting activity appeared between the utterances. In a majority of the patients the corresponding activity was markedly increased, which com-

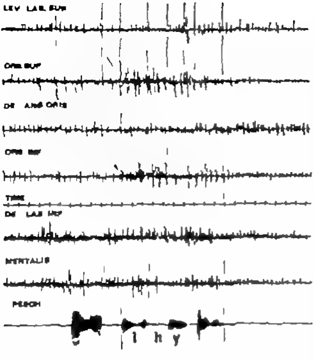


Fig 2 EMG recording from a Parkinsonian patient, showing an abnormally long anticipation period for activity in M. orb. oris sup et inf. associated with the production of [y] (*arrows*). Time scale 100 msec.

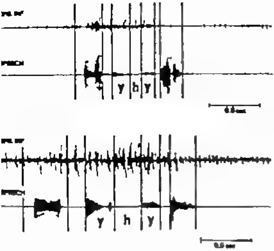
plicated the identification of the speech initiation or prespeech activity that is often present in normal-speakers (Fig. 1 left, M. lev et dep lab and M. mentalis initial portions of the traces preceding the first acoustic segment)

The intense resting activity of the patient (Fig. 1 right) merges into a sustained background activity which continues throughout the utterance. The increased background activity predominates in M. lev lab and M. dep lab Even in normal-speakers these muscles may display a certain background tonus, which has been interpreted as a sign of their function in speech posture (Leanderson et al., 1971 *a*), but this never interfered with the activity of articulation In the patients, on the other hand, the background activity was often so prominent that it became difficult to identify the superimposed articulatory activity (cf Fig. 1 right, M. lev et dep lab) Although several of the patients exhibited tremor in the limbs and the head, *resting tremor* of the lip musculature was observed electromyographically in only one case being restricted to M lev lab and M dep lab

Articulatory activity

As shown in earlier studies, the labial muscles are normally activated in two functionally antagonistic groups for the production of rounding/closing and opening/spreading speech gesture movements (Leanderson et al., 1971 *a*) This is illustrated in Fig 1 (left), in which the lip-closing M. orb oris sup., M. orb. oris inf M dep ang. oris and M. mentalis are activated for [p]-implosion, while the lip-opening M. lev lab and M. dep. lab. are inhibited. A reversed activation pattern is visible for [p]-release, with activity in M. lev lab. and M dep lab and inhibition of the lip-closing muscles. This normal separation of the labial muscles into two groups with reciprocal activation was typically disturbed in the patients. For the [p]-implosion (Fig. 1 right) there was no reciprocal inhibition of the activity in the lip openers, M lev lab and M. dep. lab

The onset of activity for the production of labial speech sounds occurred considerably earlier in the patients than in the normal-speakers. The EMG-speech latency amounts normally to about 200 msec for rounded vowels (Leanderson et al., 1971 *a*) In Fig. 2, obtained from a Parkinsonian patient, the activity for [y] in M. orb oris sup and M. orb. oris inf precedes the acoustic segment about 400 msec (arrows) Similarly a lengthening of the anticipation time was observed for stop consonants (see the activity for [p] in the lip-closing muscles in Fig 1 right). T[illegible] considerable difference in speech rate betw[illegible] the normal-speaker and the patient in Fig. 1 does not account for the longer anticipat[illegible] time often observed in Parkinsonian d[illegible] as the same phenomenon was observed i[illegible] other patients with a more normal speak[illegible] rate In normal speakers the EMG latency or "the time interval between of the EMG activity and the center of corresponding acoustic event is comparativ[illegible]



ig. 3 EMG records from M. orb. oris inf. in a nor al-speaker (upper) and a patient (lower), showing ck of context dependence of the activity for the cond [y] in the patient, compared with activity crease in the normal-speaker

nstant, irrespective of the speed of ut rance (Hirose et al., 1969)

Context dependence

When normal-speakers pronounce a VCV combination consisting of two identical vowels co-articulated with a non-labial consonant, considerably less activity appears for the second vowel than for the first. In Parkinsonian patients the activity is often much the same for both vowels or may even increase from the first to the second. This lack of context dependence is illustrated in the lower part of Fig. 3 which should be compared with the upper recording from a normal-speaker

EMG correlates to the progress of dysarthria

Fig 4 shows two recordings from the same patient at an interval of about 1 year At the first examination the patient displayed several typical Parkinsonian speech symptoms: monotonous melody monodynamic rhythm and weak phonation. In the test situation, however his articulation of labial stop consonants was normally distinct and clear This acoustic feature corresponded electromyographically (Fig. 4 left) to a relatively normal articulatory pattern, with synchronized lip-closing activity and reciprocal inhibition of the lip openers (arrows) But the EMG records also showed

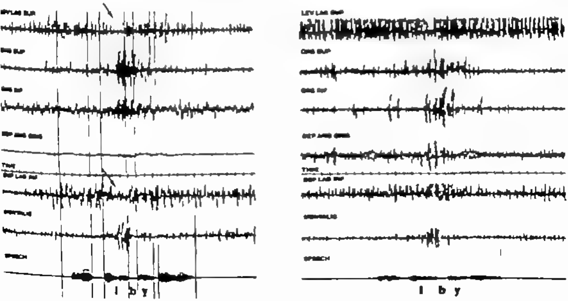


Fig 4 Two EMG recordings from the same patient with an interval of about 1 year Note inhibition of lip-opening activity at the first investigation (*arrows*). Increased background activity and impaired reciprocal activation at the second investigation (right) corresponded to an audible deterioration in the production of [b]. Time scale 100 msec.

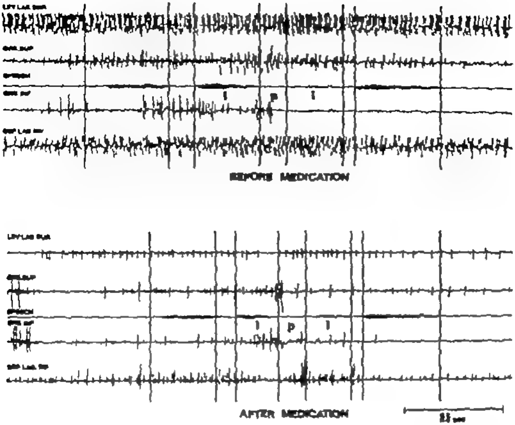


Fig. 5. Two recordings from the same patient, showing the effect of L-Dopa treatment on the EMG activity. After medication there is a decreased backgrou[nd] activity and a reestablished reciprocal activation.

typical Parkinsonian features such as increased resting and background activity and prolonged anticipation time. At the second examination the articulatory ability had deteriorated considerably and the stop consonant [b] sounded like the fricative [w]. In addition to the EMG findings at the first examination there was now a deficient reciprocal inhibition in the lip openers during [b]-implosion.

Another conspicuous change between the two recordings was the marked increase of resting and background activity, particularly in M. lev. lab. and M. dep. lab. The hypertonicity was so pronounced that it largely masked the waxing and waning articulatory pattern.

Improvement of articulatory function with L-Dopa treatment

Since the deterioration of speech with the progress of Parkinsonism corresponded to an obvious change of the labial articulatory EMG pattern, it was of interest to see whether the audible speech improvement noted after L-Dopa medication was paralleled by a malization of the EMG. As preliminari[ly] reported (Leanderson et al., 1971 *b*), af[ter] medication the articulatory activity show[ed] considerable changes towards a relatively normal pattern in all the patients. However acoustic and electromyographic improvement of articulatory function observed in the situation were more pronounced than the ef[-]fect on dysarthria in connected speech. T[he] effect of L-Dopa on the articulatory EMG i[s] demonstrated in Fig. 5. The most promi[nent] finding was the substantial reduction of th[e] intense resting and background activity ren[-]dering the articulatory activity proper readily discernible. The abnormally early o[nset] and long duration of the activity were rep[laced] by almost normal timing. Before medica[tion]

there was a typical impairment of the reciprocal activation. During [p]-implosion there was no decrease of the sustained background activity in the lip-opening M lev lab and M dep lab After medication the production of [p] was associated with a more normalized pattern, displaying an obvious reciprocal activation of antagonistic muscles.

DISCUSSION

The present investigation has shown that it was possible with the use of EMG to define some characteristic disturbances of labial articulation in Parkinsonism. Darley et al (1968) consider dysarthria to be a common denominator of the various forms of Parkinsonian speech disorder and they also claim that the articulatory errors are highly consistent in this disease. In agreement with this clinical experience, the current study showed good intra-individual reproducibility of the articulatory EMG pattern.

Compared with their disturbed spontaneous connected speech, all the patients displayed markedly improved articulatory ability in the experimental situations. This discrepancy (reflecting the difference between potential and functional speech performance) is said by Sarno (1968) to be especially apparent in Parkinsonian patients (see also Canter 1965)

The articulatory improvement in a test situation may be explained by assuming that spontaneous speech is to a great extent controlled automatically and that the dysarthria in Parkinsonism is caused by an impairment of such control mechanisms. To compensate for the loss of automatic motor control, the articulatory movements may become more dependent upon conscious effort

Although the audible articulatory performance was comparatively good in the test situation, the EMG records exhibited marked and consistent abnormalities in all the patients. Several of these abnormalities seem to reflect an impairment of the dynamic properties of the muscular system. This disturbance appears as an increased and sustained background activity predominantly in M lev lab and M dep lab

The hypertonic background activity with no distinguishable articulatory activity superimposed, impedes the participation of these muscles in articulation, thereby reducing the number of muscles available for rapid articulatory movements. The uneven distribution of tonus disturbs the functional balance between the two muscle groups for lip-closing/opening. Hyperactivity of the lip openers may even counteract the function of the lip closers. Further signs of disturbed muscular system dynamics are the abnormally long anticipation period and the lack of context dependence, both features resulting in a prolongation of the articulatory activity

EMG studies of the limb muscles in Parkinsonism have shown that one of the most characteristic signs of the motor dysfunction is an impairment of the reciprocal innervation (Hoefer & Putnam, 1940 Schaltenbrand & Hufschmidt, 1957 Schneider 1968) The current study demonstrates that the same type of disturbance may occur in the facial musculature A follow-up of one of our patients revealed a progressive articulatory deterioration of the stop consonants in particular similar to that described in several acoustic phonetic studies (Ewanowski, 1964 Canter 1967 Darley et al., 1968) Whereas a relatively well preserved reciprocal activation pattern was noted at the first EMG examination, at the second it was found that [b]-implosion involved no inhibition in the lip-opening muscles. Obviously a deficient reciprocal activation seems to be the prime factor for the misarticulation of labial stop consonants, the production of which demands rapidly alternating closing and opening speech gesture components.

The clinical improvement in the motor function of limb muscles following stereotaxic surgery in Parkinsonism is electromyographically correlated to a reestablishment of reci-

procal activation as well as a reduction of hypertonicity (Ohye et al., 1965) In the present study similar effects have been demonstrated on the articulatory function of the facial muscles as a result of L-Dopa medication

Apparently there are characteristics which are common to the impairment of motor function of Parkinsonian limb and labial musculature This is somewhat unexpected since limb muscles, being attached to the skeleton, perform joint movements, whereas labial muscles move soft tissues such as muscles and skin without necessarily having an attachment to bone Furthermore, muscles of the lips differ from those of the limbs in that they contain very few or no muscle spindles (Kadanoff 1956 Filogamo quoted by Gandiglio & Fra, 1967) Yet in spite of these important differences in functional anatomy the type of disturbance in motor control seems to be similar in both kinds of muscle This fact should be taken into consideration when discussing the neuro-muscular basis for the motor symptoms in Parkinsonism

ZUSAMMENFASSUNG

Die artikulatorische EMG-Aktivität der Lippenmuskeln wurde an Patienten mit Parkinsonismus und Dysarthrie untersucht und mit einer normalsprechenden Gruppe verglichen. Weiterhin wurde auch der Effekt einer L-Dopa-Behandlung gegen die dysarthrische Aktivitat untersucht. Obwohl sich das Artikulationsvermogen in der Untersuchungssituation verbesserte, waren doch in der EMG Aufzeichnung deutlich reproduzierbare Abnormalitaten, die sich in gleicher Weise bei allen Patienten zeigten, zu erkennen. Die Ruheaktivität zwischen den einzelnen Ausserungen war auffallend erhoht und ging oft in eine anhaltende hypertonische Untergrundaktivitat über — ein Zeichen übertriebener Sprechbeinstellung während der Ausserung. Die funktionelle Organisation der Lippenmuskeln in zwei antagonistische Gruppen für kontrastierende Bewegungen bei den Sprechgebärden war gestört; es fanden sich keine Anzeichen einer reziproken Inhibition, sondern statt dessen wurde eine Co-Kontraktion der antagonistischen Muskeln beobachtet. Zwischen diesem gestörten Aktivitätspattern und der Fehlartikulation der labialen Verschlusskonsonanten war ein deutlicher Zusammenhang feststellbar Des weiteren wurde in der EMG-Aktivität des öfteren eine verlängerte Latenzzeit und das Fehlen einer Kontextabhängigkeit beobachtet. Nach Verabfolgung von L Dopa trat eine Reduktion der Untergrundaktivität ein und die reziproke Aktivierung setzte wieder ein. Die angeführten Befunde werden abschliessend im Zusammenhang mit von anderen Verfassern veröffentlichten Daten über die Muskelfunktion der Gliedmassen bei Parkinsonismus diskutiert.

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SPONTANEOUS HEALING OF IDIOPATHIC FACIAL PARALYSIS

A Clinical and Electromyographic Study

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Abstract In 57 patients with idiopathic facial paralysis the course of spontaneous healing has been studied by electromyographic and clinical assessment. In 31 patients healing occurred without denervation, whereas 26 patients (45%) showed signs of denervation. In all 31 patients who were without any signs of denervation healing was complete. Of the 26 patients who showed signs of denervation, good functional healing occurred in 21 whereas in 5 patients (9%) there were troublesome residuals. In the therapeutic results reported in the literature, spontaneous healing was only surpassed after treatment with ACTH. The influence of operations for decompression, on denervation and reinnervation has not been clearly elucidated, and reports on unexceptionable results for operated material are lacking.

Idiopathic facial paralysis is the most usual type of peripheral facial paralysis, and its frequency is stated to be between 62% (Cawthorne & Haynes, 1956) and 86% (Lagerholm & Toremalm, 1971)

Several hypotheses as to the etiology of idiopathic facial paralysis have been advanced. At an early stage, neuritis was regarded as a common cause (Gowers, 1895). During recent decades the ischemic theory (Worms & Chams, 1931 Audibert et al. 1936) has had many adherents (Kettel 1959 Cawthorne, 1965) Still more recently the hypothesis of an infectious etiology has again become current, as it has been stated that a primary infection attacks the chorda tympani and, by retrograde spreading, reaches the main trunk of the facial nerve (Blatt & Freeman, 1966) Histopathologic investigation of nerve fragments from autopsy and resection material in connection with nerve transplantations (Kettel, 1959) have not afforded any conclusive proof of the validity of any of the theories put forward.

Therapeutic management has been charac- terized by the incomplete elucidation of etiology Evaluation of the therapeutic resul- has been dominated more by subjective ments than by objective recording and careful analyses of the healing process. An operati- decompression of the nerve in selected has been stated to give good results (Kettel 1959 Miehlke, 1960 Jongkees, 1965), as a number of authors consider that conserva- tive methods of treatment are preferable (Mi- ler 1967 Taverner et al. 1967). U- tional analyses of results have been carried only after some conventional methods of trea- ment (see Discussion).

Evaluation of different forms of treatment made more difficult by the high frequency spontaneous healing in cases of idiopathic cial paralysis. All assessments must be on a consideration of this fact. Since it is uncertain whether improved results by operative treatment (see Discussion), du- ing recent years conservative treatment been applied in the Department of Oto- logy at Karolinska sjukhuset. To facilitate evaluation of our therapeutic results the of spontaneous healing was studied in a of patients with idiopathic facial paralysis studies were made by means of precise myographic and clinical assessment, and

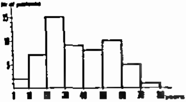

Fig. 1. Age distribution in the primary material for 57 patients with idiopathic facial paralysis.

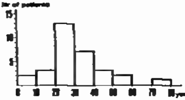

Fig. 2. Age distribution for 31 patients with idiopathic facial paralysis without signs of denervation.

purpose of this paper is to report on the results of the investigation.

MATERIAL AND METHOD

The investigation comprised 57 patients with complete idiopathic facial paralysis. The diagnosis was made at the clinical investigation, and if it was possible to determine the etiology the case was excluded.

The mean age of the 57 patients was 36.7 years; and the age distribution is shown in Fig. 1. The material contained 30 males whose mean age was 35.4 years. The age range was from 10 to 66 years. The mean age of the 27 females was 38.2 years (range, 3–78 years).

In 26 cases paralysis affected the left side and in 31 the right. Seven of the patients were clinically examined within 1 week of onset, and 52 of the 57 patients within 2 weeks. The cases were assessed and controlled by the same investigator during the entire observation period. The patients were controlled until full healing had occurred or until the course of healing was regarded as having stopped. In such cases the healing time was reckoned from the onset of paralysis up to the first of two investigations, with an interval of 1 month, when no further functional improvement was observed and electromyography (EMG) showed an unchanged reinnervation picture. Electromyography was performed parallel with the clinical assessment in order to determine the nerve injury objectively. The EMG investigation consisted in exploring the musculus frontalis, orbicularis oculi and oris with needle electrodes and assessment was made according to the usual electromyographic criteria. The occurrence of fibrillation potentials is especially valuable for the assessment of denervation. These potentials occur 7–21 days after the injury (Taverner 1955). For this reason the patients were investigated electromyographically at the earliest 2 weeks after falling ill.

Patients who at the EMG investigation presented fibrillation potentials were put in one group "the denervated" whereas the remainder were placed in a second group, "the non-denervated".

The patients did not receive any treatment other than the physical treatment of the facial musculature, which was applied, for psychological reasons, in individual cases where the course of healing was protracted.

RESULTS

The non-denervated

All patients in whom at the EMG investigation signs of denervation were lacking, were put in the "non-denervated" group. Two cases in which healing took place in the course of 2 weeks were also put in this group because of the rapid healing process. In these two cases an EMG investigation was not made since there was full clinical healing at the time planned for the EMG investigation. The "non-denervated" group consisted of 31 patients (55%) with a mean age of 30.6 years. Fig. 2 shows the age distribution of this group. In all the patients in this group healing without residuals occurred in the course of 8 weeks; the mean healing time was 24.4 days (Fig. 3).

The denervated

Electromyographic signs of denervation were observed in 26 patients (45%). The mean age of these patients was 43 years. Their age dis-

Table 1 Classification of 26 patients with signs of denervation, according to the occurrence of functional defects

Group 1 Good voluntary mobility Associated move ments may occur but are not subjectively troublesome.
Group 2. Poor voluntary mobility Troublesome associ ated movements

	Number	Percentage of entire material	Percentage of "denervated" group
Group 1	21	36.8	80.8
Group 2	5	8.8	19.2

tribution is shown in Fig. 4 Healing time varied between 6 weeks and 11 months. Be tween these limits healing time was rather evenly divided (Fig. 5)

Healing through reinnervation may cause de fects in the form of reduced mobility in one or more of the branches of the N facialis, muscle contractures, synkineses and, more rarely fa cial spasms. The results of healing have been evaluated in the denervated group and have led to the grouping shown in Table I.

The evaluation is based on the investigator's assessment of the voluntary mobility on the af fected side in relation to the mobility of the musculus orbicularis oculi, oris and frontalis on the normal side. Moreover the degree of synkinesis was recorded and when grading, the patients own estimate of the discomfort caused them by the synkineses was also taken into account.

In group 1 there was good voluntary mobi lity This group consisted of 21 patients. There were cases of distinct visible synkineses, but

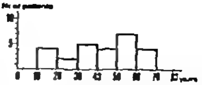

Fig 4 Age distribution for 26 patients with idiopathic facial paralysis with signs of denervation.

also those where the investigator could not de tect any healing defects. None of the patients in this group who had synkineses complained of subjective discomfort on this account. If troublesome synkineses were present or there was poor voluntary mobility the patients were put in group 2, which consisted of 5 cases. The patients in group 1 considered that healing had been satisfactory whereas those in group 2 considered they still suffered discomfort.

None of the "denervated" patients was en tirely without voluntary mobility after the heal ing process had been completed.

DISCUSSION

In the material reported on 26 patients (45%) showed signs of denervation. This agrees with earlier investigations of untreated material where the frequency of denervation had been found to be about 40% (Taverner 1959). In the non-denervated the nerve injury is probably of a neuropraxia type (Seddon, 1943) signifying a temporary transmission block with uninjured axis cylinders. This type of injury leads to rapid and complete healing. In the non-de nervated group muscular function was fully restored, on an average in 24.4 days. In the

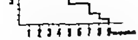

Fig 3 Healing time for 31 patients with idiopathic facial paralysis without signs of denervation.

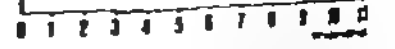

Fig 5 Healing time for 26 patients with idiopathic facial paralysis with signs of denervation.

denervated cases healing was considerably longer and the longest healing time was 11 months. In these cases the nerve damage was probably to some extent of an axonotmestic type (Seddon, 1943) where the axis cylinders had disintegrated peripherally from the site of the injury and healing had occurred by regeneration of new nerve fibres. The rate of this process is about 2 mm per day in the peripheral nerves in man (Guth, 1956) Consequently the healing process may be expected to be much longer than for injuries without denervation. These conditions are in good agreement with those reported for the present material. Healing through reinnervation may be associated with defects, but the final results need not necessarily be functionally unsatisfactory. In 21 of the 26 patients with denervation, good voluntary mobility was restored. The degree of healing in these patients was fully satisfactory both subjectively and objectively. If these 21 patients are taken together with the 31 patients who were entirely healed in the non-denervated group then satisfactory clinical healing was obtained in 52 patients (91%) Poor healing continued in 5 patients (9%). Investigations published earlier (Miller 1967) also showed that healing was unsatisfactory in about 10% of the patients.

Thus, there is a very good tendency for spontaneous healing to occur in cases of idiopathic facial paralysis. With regard to the final results, successful treatment can be expected only in a small group of patients and this causes a dilemma when analysing the results. At the same time as merely marginal results can be expected, more stringent indications must be applied, especially regarding methods of treatment involving risks.

Idiopathic facial paralysis is often treated by means of physical therapy and different medicinal procedures. A thorough evaluation of the therapeutic results has been made for cortisone treatment (Taverner 1954) and for physical therapy (Mosforth & Taverner 1958) Cervical sympathetic block has also been assessed (Fearnley et al., 1964) None of these methods of treatments has given results that surpass spontaneous healing. The only form of medicinal treatment that has shown significantly improved results is treatment with adrenocorticotrophic hormone (ACTH) (Taverner et al., 1967)

Otolaryngologists have stated that in selected cases surgery has proved valuable. In his monograph in 1959 Kettel described a follow-up study of 65 patients operated on for idiopathic facial paralysis. Twelve of them recovered normal mobility 38 had 75% mobility and 15 had 50% mobility All of them presented some degree of synkinesis. This shows that healing was due to reinnervation, which presupposes that there had been previous denervation. Other investigations have shown that once denervation occurs there will be residuals whether or not surgery is performed (Naumann et al., 1968). A recently published comparison between operated and non-operated patients with idiopathic facial paralysis of not less than 2 months duration shows that there was no difference in the results for the two groups (Münker 1971).

Previously 8 weeks after onset was suggested as the appropriate time for operating (Kettel, 1959) because subsequent healing is improbable. It is evident from the present material that several of the cases that healed through reinnervation required a long time. In recent years it has been asserted that the operation should be performed as soon as modern electrodiagnostic methods are able to demonstrate signs of denervation (Jongkees, 1965 1969) It is considered that this can be done at the earliest 7–14 days after an injury has been sustained, by determining the conduction velocity (Taverner 1965) or the excitability (Laumans, 1965) of the injured facial nerve. It is difficult to judge the results of previous decompression operations, especially because of the degree of uncertainty when determining denervation by means of the methods last mentioned. Objections have also been raised against these early operations, when denervation was held to have

8–24 hours after injury (Zillch, 1961) No statistics are available to show that the results of either early or late decompression surpass the results obtained for a comparable series of untreated, or conservatively treated patients.

To sum up it may be stated that there is documentation to show that a decompression operation after denervation has occurred, can not prevent the residuals that are also observed in untreated material. Nor is there any proof that decompression can prevent denervation. This is a question of the greatest importance for the future choice of methods of treatment for idiopathic facial paralysis. Until this question has been answered we can obtain but little improvement beyond the good spontaneous-healing tendency and the demonstrated therapeutic successes gained with ACTH (Taverner et al., 1967)

ZUSAMMENFASSUNG

An 57 Patienten mit idiopathischer Fazialisparese ist der Spontan-Heilungsverlauf mit elektromyographischer und klinischer Beurteilung studiert worden.

31 der Patienten heilten ohne Denervation aus, während 26 Patienten (45%) Denervationszeichen aufwiesen. Alle 31 Patienten ohne Denervationszeichen heilten vollständig aus. Von den 26 Patienten mit Denervationszeichen traf bei 21 eine gute, funktionelle Heilung ein, während 5 von ihnen (9%) anteude Beschwerden behielten.

In den, in der Literatur angegebenen Behandlungsitaten wird die Spontanheilung nur von denen nach ACTH Behandlung, bedeutend übertroffen. Die Einwirkung von Dekompressationsmethoden auf Denervation und Re-innervation ist nicht klar nachgewiesen, und ein einwandfreier Nachweis von Resultaten an operiertem Material fehlt ganz.

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GROWTH PATTERN OF MENINGEOMAS PENETRATING THE SKULL BASE

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Abstract. Three cases of intracranial meningeomas are presented as examples of tumours in which the extra cranial growth formed a major otorhinolaryngological problem. The infiltrative growth pattern into the narrow lamina and bone channels of the otherwise histologically benign tumours is compared with findings in an experimental organ culture system, where a three-dimensional fibrin foam matrix formed the supporting structure with an interconnected network of lacunae. Of all intracranial tumours, meningeomas are the best growers in the system, and the clinical relevance of such growth characteristics demonstrated in vitro is pointed out in view of the presented cases.

Benign intracranial meningeomas are well known to be sometimes associated with extrameningeal growth that penetrates the laminae of the bony skull by direct continuity (Kernohan & Sayre, 1952 Faulwetter 1959) and may extend to the surrounding exterior tissues and paranasal sinuses (Belal, 1955 Ash et al. 1964) Such tumours are mostly associated with the normal foramina of the skull and the vertebral column. The origin of meningeomas is believed to be in the arachnoid fibroblasts although the earlier German literature also advanced the possible endothelial etiology of these neoplasms (Schmidtmann, 1928) In any case, arachnoid fibroblastic cell clusters can also occur in the dura, and these nests may presumably protrude through the dura and participate in the tumour formation, thus giving rise to the extradural growth (Lindström & Lindström 1969). Actual defects in the dural lining may occur in association with various operative procedures of the skull, providing pathways for extradural spread of meningeomas. True infiltrative growth of the meningeomas through the dura, therefore, apparently need not be implicated. However the growth of these tumours in the surrounding tissues, particularly in the bone very closely mimics infiltrative growth pattern, as observed in histological sections, although no other evidence of histological malignancy nor clinical behaviour compatible with malignant character is present.

In the present report we describe three cases of intracranial meningeoma associated with extradural growth, and relate the growth pattern to experimental work in three-dimensional organ culture system in order to illustrate this particular propensity of meningeomas.

This work was supported by grants from the Sigrid Jusélius Foundation, and the National Council for Medical Sciences, Finland.

Clinical histories

Case 1 64-year-old female, on whom a right frontal craniotomy was performed in 1967 because of an olfactory meningeoma. The tumour was located mainly in the right frontal fossa. The tumour weighing 22 g was totally removed and the adherent dural surface was electrocoagulated. At the end of the operation the base of the skull was noted to be intact. In histological examination the diagnosis of

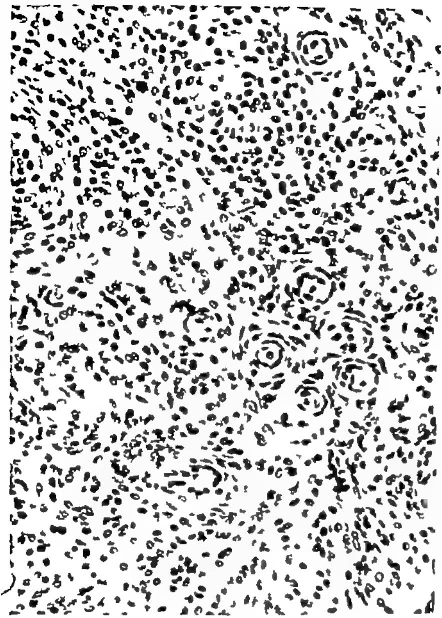


Fig 1 Meningotheliai meningeoma growing in the mucosa of maxillary sinus of patient 1 Note the characteristic whorls and regular cellular morphology (Hematoxylin eosin, 190)

a meningeoma was made Two and a half years later the patient was admitted to a hospital because of nasal obstruction due to tumour growth. The nasal cavity and the paranasal sinuses were opened and a tumour of approximately 5 × 7 × 7 cm was extirpated. The stilus of the tumour was adherent to lamina cribrosa, which appeared normal on inspection. The tumour had penetrated the dilated foramina of lamina cribrosa and grown to the right nasal cavity ethmoidal sinus, and partly to the sphenoidal sinus. The whole tumour mass was removed and no recurrences have be noted since.

Case 2 A 38-year-old female whose histo logically verified meningeoma was operat from the right orbita in 1966 A recurre tumour was extirpated in 1970 from the rig orbita and later the same year tumour tis was extirpated from the ethmoidal and sph noidal sinuses. There was a third recurre during the same year and a craniotomy tumour mass the size of a tangerine was r

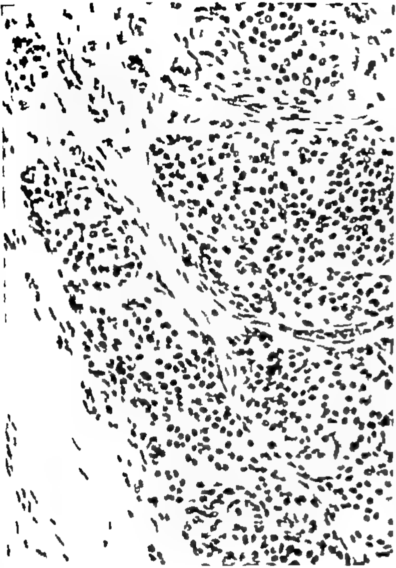
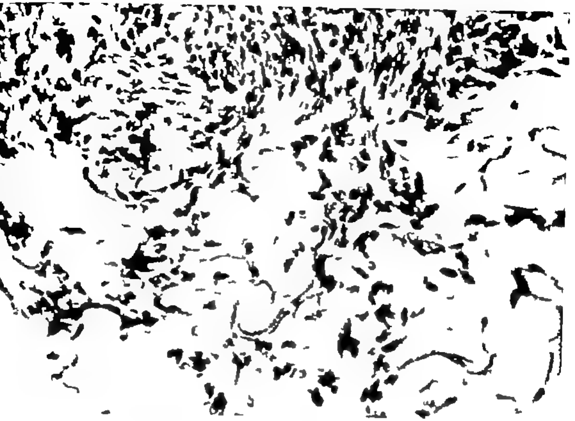


Fig Infiltrative growth pattern of a meningothelial meningeoma (same patient as in Fig 1) (Hematoxylin eosin, 150.)

moved, extending from the right frontal fossa to the orbita. Some tumour tissue was left, and further recurrences are expected.

Case 3 In 1961 when the patient was 14 years old, a large intracranial tumour filling the whole frontal fossa was removed. The tumour was histologically diagnosed as a benign meningeoma, but it could not be entirely removed since the growth had penetrated the bone and extended to the orbita. In 1968 a recurrence weighing 90 g was removed from the frontal fossa. Penetration to the bone and left orbita was again noted and because of increasing protrusion of the left eye, an orbitomy was performed during the same year and as much tumour tissue as possible removed. In 1969 and 1970 similar plastic operations of the orbita have been performed because of recurrent protrusion of the left eye due to tumour growth. After each operation the functional state of the eye has been restored and all the ocular muscles have performed normally postoperatively. After the last operation the visus was 1 0.



g. 5 A fibromatous meningeoma growing into a ...dia foam matrix structure in an *in vitro* organ ...ture system. The explant is visible at the top of the figure and the growth penetrates the overmost layers of the lacunae. (Hematoxylin eosin, × 150.)

...istological findings

...n cases 1 and 2, the specimens were from ...e maxillary sinus, where the tumour grew ...s a lobulated mass in the submucosa. The ...ze of the lobules varied greatly and had ...ometimes a tendency to separation. In both ...ses the cells were arranged in cords and ...lands, which frequently showed a whorled ...attern and psammoma-like concentric ar-...angement. In case 1 the latter feature was ...ost prominent (Figs. 1, 2). The nuclei were ...void, regular and vesicular. Very little varia-...on was apparent in the nuclear size and ...hape. No mitoses were seen. Cytoplasmic ...orders were indistinct and no calcification ...as present. The picture was characteristic ...r the diagnosis of benign meningothelial ...eningeoma.

In case 3 sections were obtained both from the frontal bone and from the mucosa of the sphenoid sinus. The tumour grew in the lacunae of the bony matrix in islands and groups where the cells were mostly elongated, fibroblastic and arranged in criss-crossing bundles or when more epithelioid, in relatively solid sheets (Figs. 3, 4). Psammoma-like structures were not present. The nuclear size was often variable and some multinuclear cell forms were seen. The staining of the chromatin also varied somewhat, but no mitoses were seen. The histological sections were compatible with the diagnosis of fibromatous meningeoma. The same morphological pattern was seen in the sections taken from the mucosa of the sphenoid sinus.

Fig. 6. A meningothelial variety of meningeoma growing in the organ culture as above. Note the reproduction of the original histogenetic structure with the lacunae at the left. (Hematoxylin eosin, 150.)

Growth of meningeomas in vitro compared with other human brain tumours

e carried out a series of experiments utilizing vitro techniques (Holmström et al., 1970 mström & Saksela, 1971) and various human brain tumours in order to register their growth capacity in a three-dimensional organ culture system. Human benign and malignant brain tumours (fibromatous meningeomas, meningotheliomatous meningeomas, neurinomas and gliomas) were cut in sterile manner into small pieces of about 1 mm³ and explanted on small cubes of porous human fibrin foam in Petri dishes. As nutrient medium BME supplement with 10% fresh autologous serum and antibiotics was used. The medium was added to the upper level of the fibrin foam so that the tumour explant was located at the gas-liquid interphase. The culture dishes were incubated at 37 C in humidified atmosphere of 5% CO_2 in air for 3–14 days, and ³H thymidine was added to the medium for the last 2 hours. The cultures were fixed in Carnoy solution, embedded in paraffin and serially sectioned at a 90 angle to the surface of the fibrin foam piece. Staining was performed with acetic orcein. In microscopic analysis of the growth of the tumour explants, the penetration of tumour cells from the explants to the pores and lacunae of the fibrin foam matrix was estimated autoradiographically and by measuring the number of pore layers that the growth had penetrated. In many cases the tumour cells filled the lumina of the lacunae completely and reproduced the original histological structures of the tumours (Figs. 5, 6).

Figure 7 shows growth characteristics relevant for the present discussion. The fibroma-

tous meningeomas were the most active growers in the system used. They penetrated most deeply into the lacunae of the fibrin foam matrix, even deeper than the malignant gliomas. The meningotheliomatous meningeomas behaved in a fashion more similar to the latter but the average degree of penetration into the fibrin foam structure was significantly higher than in the other tumour groups. The uptake of tritiated thymidine in autoradiography indicated that true cellular proliferation was in question, in contrast to a possible passive locomotion or dropping of the cells into the lacunae (Holmström et al. 1970).

Concluding remarks

The three reported cases represent examples of intracranial meningeomas where the extracranial growth of the tumour formed a major otorhinolaryngological problem. In case 1 an intracranial olfactory meningeoma manifested its extracranial extension 2.5 years later by growth through the foramina of lamina cribrosa to nasal cavity and paranasal sinuses. In case 2 the tumour grew into the air cells of the ethmoid and sphenoid bones, and in case 3 the tumour growth invaded the Haversian system of the adjacent bone extending to the orbita. In this latter case a characteristic hyperostotic lesion was seen, where the absorption and regeneration of bone formed a tumourous mass, which enabled a preoperative X-ray diagnosis of intraosseal penetration of the tumour (Fig 8). In two of the cases the course of the disease was characterized by frequent recurrences that rendered the surgical control of the disease difficult, and at the present moment the final outcome is uncertain.

Histologically the growth pattern very closely mimicked infiltrative growth, although no other signs of histological malignancy were present. Basically the tumours may be considered to represent benign neoplasms still in their active growth period where the "steady

Fig 8 An X-ray picture of the frontal bone of patient 3 showing the tumour growth invading the adjacent bone. Note the characteristic hyperostotic reaction

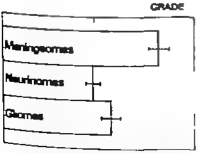


Fig 7 Growth of the various human brain tumours in the three-dimensional organ culture system. Average degree of penetration into the lacunae of the matrix and the standard deviations are indicated.

state" is still to be achieved. The particular difficulty resides in the propensity of the tumours to invade the narrow lumina and channels of the adjacent bone and extracranial structures. The point that we wish to make is that this pattern could be reproduced in experimental conditions when a number of intracranial tumours were compared in an organ culture system where the supporting matrix provided the network of interconnected lacunae. Under these conditions, the meningeomas, especially the fibromatous meningeomas, were set significantly apart from all other intracranial neoplasms in their capacity to invade the lacunae of the fibrin foam in the Trowell-type organ culture system. These findings agree with the behaviour of the reported three clinical cases, of which case 3, a fibromatous meningeoma, was clinically most aggressive. The well known infiltrative growth capacity of the meningeomatous cells into surrounding bone may be an inherent characteristic of the tumour reproducible under the in vitro conditions. Closer analysis of the basic cellular properties underlying this lack of restricted growth control in an otherwise apparently benign tumour may be possible with the organ culture systems utilized. The findings illustrate at least in this particular case the relevance of the in vitro characteristics of tumours to their clinical behaviour.

ZUSAMMENFASSUNG

Es werden drei Fälle von intrakraniellem Meningeom als Beispiele von Tumoren beschrieben, in denen das extrakraniale Wachstum ein großes otorhinolaryngologisches Problem ausmacht. Die infiltrative Wachstumsweise des sonst histologisch benignen Tumors in die engen Lumina und Knochenkanäle wird verglichen mit Befunden in einer experimentellen Organkultur wo ein dreidimensionaler Fibrinschwamm die tragende Struktur mit einem zusammenhängenden Netzwerk von Lakunen darstellt. Von allen intrakranialen Tumoren wuchsen die Meningeome am besten in diesem System. Die klinische Bedeutung dieser in vitro nachgewiesenen Wachstumsweise wird im Hinblick auf die beschriebenen Meningeom-Fälle hervorgehoben.

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ADENOTOMY ANTROSTOMY AND CALDWELL LUC OPERATION IN THE TREATMENT OF CHRONIC BRONCHITIS IN CHILDREN

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Abstract. The study is based on 45 children with chronic bronchitis. Their ages varied between – and 15 years, the average being 8 years 6 months. 44 children had diseases of the nose, paranasal sinuses or nasopharynx. Adenotomy was performed on 42 children and 16 of these were helped by this operation. In 22 cases intranasal antrostomy was made in the inferior meatus with a good or satisfactory result in 14. The Caldwell-Luc operation, performed on 14 children, had a good or satisfactory effect on both sinusitis and bronchitis in all cases thus treated.

The nose, nasopharynx and bronchial system are parts of one functional unit. The division into upper and lower airways has been quite arbitrary and essentially a didactic one (Minnigerode, 1969) In the presence of coincidental sinusitis and bronchitis, the patient is said to suffer from sinobronchial syndrome, the pathogenesis of which is not known. Rhinobronchial or descending infection is generally considered to be far more prominent than bronchorhinological or ascending infection, i.e. infection of the sinuses by way of the bronchi (Naumann. 1970). However even assuming that bronchitis develops from nasal and nasopharyngeal infections it is known whether the bronchi are infected via sinus secretions or whether the infection has spread along neural pathways or by allergy (Minnigerode, 1969).

Chronic bronchitis in children refers to a condition attended by productive cough presenting expectoration with pus for 3–6 months or recurrent episodes of productive cough. To settle diagnosis, however there must be changes indicating chronic bronchitis on bronchoscopy biopsy examination of bronchial mucosa and bronchography Sinusitis quite often accompanies chronic bronchitis in children. the incidence was 46% in the series of Murakami et al. (1971) and 71% in that of Kubo et al. (1971)

Forty-five children with chronic bronchitis were treated at the Children's Hospital, University of Helsinki, during the period 1965–1970 The examinations, treatment and evaluation of results were entrusted to one permanent team, which included two pediatricians (one of them also an allergologist), a chest surgeon, a roentgenologist, and an otorhinolaryngologist. The method of and findings at examination, the treatment methods and results of treatment will be reported on in detail at a later date. Below the lines followed in the surgical treatment and the results hitherto obtained are dealt with as far as the nose nasopharynx and maxillary sinuses are concerned.

Clinical observations

Age and sex The total of 45 children included 21 boys and 24 girls. Ages at admission varied from 2 years to 15 years 6 months, the mean being 8 years 6 months.

The rhinological history showed that 26 pa

Table I *Severity of bronchitis in children with chronic bronchitis as evaluated by the bronchoscopist 42 children*

Stage of severity examination	No. of cases
No bronchitis	3
Slight bronchitis	10
Moderately severe bronchitis	27
Severe bronchitis	2

tients (57%) had been operated on elsewhere for adenoids, and sinusitis had been treated conservatively in 16 cases, 14 of which belonged to the above group of adenoid operations.

X rays of the paranasal sinuses showed changes indicating sinusitis in 39 of the patients, or 86% The maxillary sinuses were densely opaque in 13 children None presented fluid levels. Adenoids were seen in X-rays in 21 cases in 5 of these adenoids had grown again after a previous operation

The degree of severity of the bronchitis evaluated by the bronchoscopist was in 42 cases as follows (Table I) In 3 cases no such evaluation was made.

As will be seen, there were 3 cases with no distinct macroscopical evidence of chronic bronchitis. The majority belonged to the group of moderately severe bronchitis. One of the 2 patients with severe bronchitis had atrophic rhinitis.

The micro-organisms cultured from bronchial and nasal smears are shown in Table II.

Table II *Bacteria cultured from bronchial secretion and nasal smear in 45 children with chronic bronchitis*

	No of cases	
Organism	Bronchial secretion	Nasal smear
Staphylococcus aureus	4	9
Streptococcus beta-hemol	4	
Diplococcus pneumoniae	11	9
Hemophilus influenzae	15	9
No organisms	13	21

Table III *Effect of adenotomy in cases of chronic bronchitis 47 operated children*

	No of cases	Symptom-free or Mild symptoms No. of cases	
Adenotomy performed elsewhere before team took over treatment	26	6	
Adenotomy performed by team (5 readenotomies included)	21	10	
		Symptom-free	Mild symptoms
		5	11

Although the bacteria obtained were the same, there were only 2 cases in which the same bacterial strain was present at the same time in bronchial secretion and in the nasal smear The bacterial findings did not permit any definite conclusions to be drawn as regards the occurrence of sinusitis or bronchitis. Nasal cytograms revealed allergy in 5 cases and atrophic rhinitis in 2 cases. In all others the cytogram showed infection

SURGICAL TREATMENT AND PRELIMINARY RESULTS IN 44 CHILDREN

Surgical treatment

Only 1 patient, a boy of 12, was not subjected to any nasal operation

Principles followed in rhinological operations. When adenoids were diagnosed, adenotomy was performed regardless of whether a simultaneous sinusitis was present or not. During the years 1965–1968, maxillary sinus punctures and irrigations were carried out but these were later abandoned because they were found to be of only diagnostic value

If the bronchitis did not show any signs of cure after adenotomy and there were still changes indicating sinusitis in the X-ray at 3–6 months after adenotomy intranasal an-

trostomy was resorted to and performed in the inferior meatus. At the same time a specimen of maxillary mucosa was removed for biopsy examination. Afterwards the patients presented themselves for tests at the hospital and their recovery from bronchitis and sinusitis was thus followed. Depending on the results of maxillary biopsy examinations, antrostomy could be repeated once or twice if the openings closed.

In cases in which sinusitis persisted and there were no signs of recovery from bronchitis, the maxillary mucosa indicating chronic inflammation, i.e. fibrosis of the subepithelial layer and partial disappearance of cilia in the epithelium, were decided in favour of radical removal of the maxillary mucosa using the Caldwell-Luc operation. This operation was performed in a few cases without being preceded by an antrostomy (after adenotomy) if the bronchoscopic and bronchographic changes were of markedly severe degree

Results

The results of adenotomy appear in Table III As seen from the table adenotomy was helpful in 16 cases out of 42. The results of antrostomy are shown in Table IV

Antrostomy proved useful in 14 cases out of 22 but was of no avail in 8 The results of the Caldwell-Luc operation are presented in Table V

The operative results are found to be relatively good in the Caldwell-Luc group

The findings in Tables III–V may be summarized by stating that cure was obtained by adenotomy alone in 16 cases, by antrostomy in 14 cases, whereas the Caldwell-Luc operation resulted in cure in all the 14 cases.

Table IV *Effect of intranasal antrostomy in the cases of chronic bronchitis, 22 operated children*

	No. of cases	Symptom-free	Mild symptoms
Antrostomy	22	3	11

Table V *Effect of Caldwell–Luc operation in the cases of chronic bronchitis 14 operated children*

	No. of cases	Symptom-free	Mild symptoms
Caldwell–Luc operation (previous antrostomy in 8 cases and previous adenotomy in 6 cases)	14	2	12

DISCUSSION

The above report deals with the frequency of certain rhinological operations and with the preliminary results obtained by the various operations in 44 children suffering from chronic bronchitis. At this stage it is difficult to say accurately how many of the patients will recover totally and what part the surgical procedure will play in the recovery It should be kept in mind that the therapy included treatment for acute respiratory infections, notably recurrent ones, prolonged courses of antibiotics, expectorants, physical rehabilitation, and various vaccinations.

With *adenotomy* a satisfactory result was obtained in 16 of 42 children thus operated on (38%) When studying the relationships between adenoids and sinusitis in children Huggill & Ballantyne (1952) found that sinusitis had been cured in 82% of the cases by means of adenotomy alone. The use of maxillary puncture together with adenotomy did not improve the results, sinusitis was cured in 75% of the cases. The coincidental occurrence of sinusitis and chronic bronchitis seems to make cure of sinusitis much more difficult since it proved necessary in 28 of our 44 cases (63) to make a maxillary operation.

Antrostomy yielded a satisfactory result in 14 of 22 children thus operated upon (63%) This result is in agreement with that obtained by Tarkkanen et al. (1969) in a follow-up study of adults and children operated on by antrostomy There have been many adverse reports recently on antrostomies made in the inferior meatus Macbeth (1968) states that it is one of the biggest fallacies in rhinology that an intranasal antrostomy made in the inferior

meatus drains anything it cannot do so because the ciliary stream is directed towards the ostium opening into the middle meatus. True according to Macbeth, it is a more important reason for the frequent failure of the intranasal window that irreversible changes have already occurred in the lining membrane of the antrum and, although the ciliation remains for a long time it cannot cope adequately with the continuing infection of mucoid secretion. Lavelle & Harrison (1971) recommend middle meatal antrostomy because it is a simpler procedure than other antral operations and because most cases with maxillary sinus infection appear to respond better to antrostomy in the middle meatus than to the conventional Caldwell Luc operation In our opinion middle meatal antrostomy on young children, for instance 2–3 years old, should be performed under visual control, i.e the maxillary sinus should be opened from the fossa canina, in order to ensure that the instrument enters the sinus and does not injure the orbit and eye

Middle meatal antrostomy might be supplemented with long-term intubation of the maxillary sinus—a treatment with which Kortekangas (1971) reported good results. Long term intubation of the sinus ostium should always be based on tests of the patency of the ostium. The rhinomanometric equipment required for these tests was not available in our hospital during the years 1965–1970

The Caldwell Luc Operation was resorted to in 14 cases, 9 girls and 5 boys, varying in age from 5 years and 11 months to 15 years. The average age was 8 years and 11 months, and thus nearly the same as the figure for the total series. The effect of this operation on the development of the permanent teeth and the maxilla as a whole will only be revealed by future follow-up studies.

The decision to perform a Caldwell Luc operation was always carefully preconsidered. The condition of the patients could be described as a vicious circle, which we think was successfully interrupted by this operation

Our preliminary results support the theory that rhinogenic factors play the most prominent part in the origin of sinobronchitis. But what we do not know at the present time is why chronic bronchitis develops only in a small proportion of the children having adenoids and sinusitis.

ZUSAMMENFASSUNG

Die Untersuchung umfasst 45 Kinder mit chronischer Bronchitis. Die Altersverteilung lag zwischen ? und 15 Jahren mit einem Durchschnittsalter von 8 … 6 Monaten. Affektionen der Nase, Nebenhöhlen des Nasopharynx lagen bei 44 vor Eine … wurde bei 42 vorgenommen. Bei 16 wirkte sich … Eingriff positiv aus. Eine intranasale An… durch das Meatus nasi inferior wurde an 22 geführt. Bei 14 wurde ein gutes oder befried… Resultat erzielt. Eine Caldwell Luc Operation … flusste bei allen 14 Kindern sowohl die Sinusitis auch die Bronchitis gut oder befriedigend.

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PIVAMPICILLIN (PONDOCILLIN®) IN THE TREATMENT OF MAXILLARY SINUSITIS

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Abstract Systemic antibiotics appear to have only a doubtful or slight effect on recovery from sinusitis. Since it has been demonstrated that a sufficient tissue level of ampicillin should be expected in the mucosa of the maxillary sinus following a new peroral ampicillin derivative, pivampicillin (Pondocillin®), some effect would be expected in the treatment of cases of maxillary sinusitis caused by sensitive bacteria. In a double blind study of cases with acute, subacute or chronic maxillary sinusitis without fever 45 patients were treated with pivampicillin, 356 mg four times daily nasal decongestant and daily lavage, and 55 patients with placebo, decongestant and daily lavage The trial disclosed a difference in the average recovery time of 0.9 days. This difference is not significant. The treatment had to be discontinued in 3 patients in the pivampicillin treated group, as the patients developed urticaria, nausea or abdominal pain and diarrhoea. However discontinuance was also necessary in one patient in the control group, due to the same side effects.

The aim of this investigation has been to examine the possible effect of pivampicillin in the treatment of acute subacute or chronic maxillary sinusitis.

REVIEW OF THE LITERATURE

Systemic antibiotics are commonly used in the treatment of sinusitis. It is generally supposed that they have some effect on complications such as osteitis, subperiorbital abscesses or intracranial spread, or in avoiding these complications. However the effect on the recovery from maxillary sinusitis itself seems to be doubtful or slight.

In a study comparing the effect of oxytetracycline with that obtained by using procaine penicillin, Lumio (1956) found that the group treated with oxytetracycline recovered more rapidly Reynolds et al. (1964) were also able to demonstrate an earlier recovery in series treated with penicillin V tetracycline or erythromycin if bacteriological examination disclosed sensitivity to the antibiotic given. In agreement with this, Axelsson et al. (1970) were able to demonstrate in cases of acute sinusitis a better effect of a treatment consisting of nasal decongestant and antral lavages or penicillin V than that obtained by decongestant only An even more rapid recovery was demonstrated, when treatment with decongestant was combined with lincomycin.

In contrast to this, Kortekangas (1963 1965) was unable to find any statistically significant effect of treatment using penicillin V penicillin G chloramphenicol, tetracycline or ampicillin respectively Nor were Jeppesen & Schaldemose (1970) able to demonstrate any significant effect of doxycycline.

Antibiotics in sinus mucosa

Lundberg et al. (1969) found 0–4 IU/g following intramuscular administration of 1.2 mill. IU twice daily of benzylpenicillin procaine in the antral mucosa. The tissue level of ampicillin in the mucosa of the maxillary sinus was 1 67 $\mu g/g$ following intramuscular administration of ampicillin sodium 250 mg and a similar level would be expected following pivampicillin 356 mg given perorally (Jeppesen & Illum, 1972)

Sensitivity of the bacteria

If this tissue level is compared with the in vitro sensitivity of many strains of pathogenetic bacteria (Rolinson & Stevens, 1961 Sutherland & Rolinson, 1964 Williamson, 1968) it can be

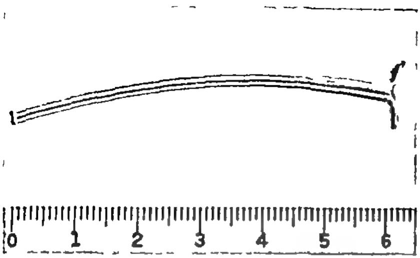

Fig 1 Polyethylene tube used for intubation of the maxillary sinus. Scale in cm.

seen that the concentration of ampicillin obtained is higher than the minimum inhibitory concentration for *Pneumococci Haemophilus influenzae* many sensitive strains of *Staphylococci Streptococci E coli* and *Proteus mirabilis* These bacteria are those most frequently seen in cases of sinusitis (Björkwall, 1950 Lystad et al., 1963 Kortekangas, 1963)

Some effect of pivampicillin in the treatment of sinusitis, caused by the above-mentioned sensitive bacteria, may then be expected.

Pharmacology

Pivampicillin the pivaloyloxymethylester of ampicillin, is used as the hydrochloride salt llin®) for oral administration. It is idly and efficiently absorbed from the stomach and the upper part of the small intestine and even when given in connection with a meal the absorption is almost unaffected. It is promptly hydrolyzed in the mucosa by enzymes present in the tissue and serum forming ampicillin. The peak serum level of ampicillin is therefore two to three times as high as that following peroral administration of ampicillin acid giving nearly the same serum level curve as that following intramuscular administration of a chemically equivalent dose of ampicillin sodium. The amount of ampicillin excreted in the urine in 0–6 hours averages 70 % of the dose given (Foltz et al., 1970 Daehne et al. 1970)

OWN INVESTIGATIONS

Methods

All patients suffering from acute subacute or chronic maxillary sinusitis seen in the outpatient clinic of or in the Dept. of Otolaryngology in the period under study were included in the trial. However all those who were allergic to penicillin pregnant suffering from diabetes mellitus severe anaemia or malignant diseases were excluded. All patients suffering from acute sinusitis with fever or frontal sinusitis, complication to sinusitis or other severe infections needing parenteral antibiotics immediately were excluded as the trial setup included a group to be treated with placebo. In addition, children under 5 years of age were also excluded because of the difficulty in swallowing the capsules.

The diagnosis was based on a careful history clinical examination roentgen examination in five standard projections and discov of mucopurulent secretion, oedema and dil vessels in the mucosa during sinoscopy (Ill & Jeppesen 1972).

Bacteriology

A sample of the antral secretion was under sterile conditions during sinoscopy specimen kept in Stuart medium was ferred immediately to the Dept. of Bacteriology for further examination including

Fig. 2. Daily lavage through the inserted polyethylene tube.

analysis of the sensitivity to ampicillin using the conventional technique.

Treatment

A sample of the mucosa was removed for histological examination during sinoscopy and finally a split polyethylene tube for daily lavage was inserted through the cannula used to puncture the inferior meatus prior to sinoscopy (Knudstrup 1970) (Figs. 1, 2). All patients were treated with a nasal decongestant (ephedrinechloride) and daily lavage and random 2 capsules each containing pivampicillin 178 mg or placebo four times daily with a glass of milk. Children under 10 years of age, however, were only treated with pivampicillin 178 mg four times a day. The study was carried out as a double blind trial.

The treatment with decongestant and pivampicillin/placebo was continued for at least 7 days and for a minimum of 2 days after secretion and therefore lavage had stopped. The treatment was only interrupted earlier in cases having severe side effects. Patients who did not recover within 30 days were excluded from the analysis of the material as other treatment then was considered necessary.

Complicating conditions

Conditions such as adenoids, nasal polyps or hypertrophic turbinates, which are generally accepted as being a disposing or aggravating factor were treated on the first day of treatment. Allergy disclosed by history or clinical examination and eosinophilia shown by blood count and/or positive intradermal exposure tests were treated with dexchlorphenramin (Polaramin dupl.®) in addition.

Side effects

Any nausea, vomiting, abdominal pains, diarrhoea or urticaria occurring during treatment were registered. The following tests: Haemoglobin, sedimentation rate, blood count, eosinophilic leucocytes, GP-transaminase, creatinine and albuminuria were performed before and controlled after treatment.

Follow up examination

This was carried out 2 weeks after recovery and removal of the polyethylene tube, and included questioning the patient with regard to any complaints, together with clinical and roentgen examination.

MATERIAL

The series comprises 45 patients in whom 65 sinuses were affected in the group treated with pivampicillin, and 55 patients in whom 87 sinuses were affected in the control group.

The material distribution according to sex,

Table I *Series*

	Pivampicillin-treated group	Control group	Total	χ^2 $p = 0.05$
No. of sinuses	63	79	142	
Sex ♀	27	34	61	0.02
♂	36	45	81	
Age				
6–10 years	7	8	15	
11–30 years	24	37	61	2.03
31–50 years	18	15	33	
> 50 years	14	19	33	
Duration of complaints				
0– < 3 weeks	9	17	26	
3– < 8 weeks	11	18	29	3.85
> 8 weeks	38	4_	80	
unregistered	5	2	7	
Frequency of earlier attacks per year				
≤ 2 attacks	33	34	67	0.88
≥ 3 attacks	30	45	75	
Ostial resistance first day				
> 20 mmHg	5	7	12	0.01
≤ 20 mmHg	58	72	130	
Bacteria				
demonstrated	13	26	39	_.07
not demonstrated	50	53	103	
Complicating diseases				
present	38	37	75	2.04
not present	25	42	67	

Table II *Bacteria present in secretions*

Parentheses denote confidence limits, p 0.05

	Pivampicillin-treated group (no. of sinuses)	Control group (no. of sinuses)
Pneumococci	4	7
α-haemolytic streptococci	1	0
β-haemolytic streptococci	3	0
Haemophilus influenzae	1	7
Pneumococci + Haemophilus influenzae	2	0
Enterobacter cloacae M.I.C. < 1.6 μg/ml	0	1
Corynebacteria M.I.C. < 1.6 μg/ml	0	
Staphylococcus aureus M.I.C.	1 < 1.6 μg/ml	3 > 1.6 μg/ml
Bacterium anitratum M.I.C. > 1.6 μg/ml	1	
Enterobacter cloacae M.I.C. > 1.6 μg/ml	0	1
Pseudomonas aeruginosa M.I.C. > 1.6 μg/ml	0	
Staphylococcus aureus M.I.C. < 1.6 μg/ml + *Pseudomonas aeruginosa* M.I.C. > 1.6 μg/ml	0	1
Total	13	26
No. of sinuses with bacteria with M.I.C. > 1.6 μg/ml	1 1.6 (0–8.5)	9 11.4 (5.3–20.5 %)

age, duration of complaints, the frequency of previous attacks, demonstration of bacteria, ostial resistance against lavage on the first day of treatment (Drettner 1966) and complicating diseases such as adenoids, anaemia, septal deviation, hypertrophic turbinates, atrophic hyperplastic or polypoid rhinitis or vasomotor rhinitis (Table I). The distribution according to these criteria is identical in the two groups ($p = 0.05$).

Bacteriology

The bacteria cultured from the sinus secretions are listed in Table II. The frequency of sinuses from which one or more bacteria with a minimal inhibitory concentration 1.6 μg/ml were found was 1.6 (confidence limits 0–8.5%, $p = 0.05$) in the pivampicillin-treated group and 11.4 (confidence limits 5.3–20.5%, $p = 0.05$) in the control group. Thus there was no statistical evidence of difference between the two groups as far as this concerns either. The groups are therefore comparable.

The frequency of cases treated with antibiotics prior to being admitted to the trial is similar in both groups (Table VII).

RESULTS

It was necessary to exclude from the following analyses one patient with bilateral disease from

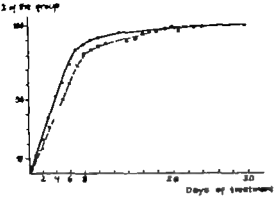

Fig. 3 Recovery time. ●—● Pivampicillin-treated group ○---○ Control group.

Table III *Average recovery time, in days*

	Pivampicillin-treated group			Control group		
	n	$\bar{x}$	$s_{\bar{x}}$	n	$\bar{x}$	$s_{\bar{x}}$
Total series (no. of sinuses)	[illegible]	5.54	0.65	79	6.42	0.54
Sex ♀	27	6 04	1.07	34	6.56	0 85
♂	36	5.17	0.82	45	6.31	0 71
Age						
6–10 years	7	7.86	3.69	8	6.38	1 43
11 30 years	24	4.87	0.47	37	5 16	0.54
31 50 years	18	5.67	0.84	15	7.87	1 42
> 50 years	14	5.14	1 99	[illegible]	7 74	1.50
Duration of complaints						
0–< 3 weeks	9	5.89	0.72	17	0.06	1 12
3–< 8 weeks	11	3.00	0 69	18	5.06	0.59
≥ 8 weeks	38	5.97	0.98	42	7 26	0.87
not known	5			2		
Frequency of earlier attacks per year						
< 2 attacks	33	5.21	0 53	34	6.65	0 73
≥ 3 attacks	30	5.93	1.24	45	6.18	0 79
Ostial resistance first day						
> 20 mm Hg	5	6.00	1 38	7	8 14	1.30
< 20 mm Hg	58	5.50	0.70	72	6.25	0.58
Bacteria						
demonstrated	13	6 69	2.05	26	6.85	0.91
not demonstrated	50	5.[illegible]4	0.63	53	6 21	0.68
Complicating disease						
present	38	6.9[illegible]	0 80	37	6.59	0.85
not present	[illegible]	5.04	0.64	42	6.[illegible]6	0.70

Table IV *Follow up examination. Complaints*

Parentheses denote confidence limits. $p = 0.05$

	Pivampicillin treated group (no. of sinuses)	Control group (no. of sinuses)
Improved	57 90.9 % (80.4–96.4 %)	75 94.9 % (87.5–98 6 %)
Unchanged or worse	6 9 1 % (3 6–19 6 %)	4 5.1 (1 4–12.5 %)
	[illegible]	79

the pivampicillin-treated group (3 1% of the total group confidence limits 0 4–10 7% $p = 0\ 05$) and 2 patients with a total of three sinuses affected from the control group (3 7% of the total group, confidence limits 0.8–10.3% $p = 0.05$) as the treatment given did not succeed within 30 days. The difference is not significant.

An average recovery time of 5.5 days was found in the group treated with pivampicillin against 6 4 days in the control group This dif ference is not significant ($p > 0\ 05$). The recovery time curve is shown in Fig. 3

An analysis of the material has therefore been carried out in order to exclude groups in which a longer recovery time could be ex pected (Table III) However none of the groups obtained by that means showed a significantly shorter recovery time.

Follow up examination

The frequency with which the symptoms disappeared or returned are shown in Table IV There is no significant difference between the two groups ($p > 0\ 05$) All 6 cases with re curring symptoms in the pivampicillin-treated group have often previously had recurring at tacks, and in 2 cases the treatment was required for 30 days before the patients became free from symptoms. In the control group one had had recurrent disease earlier and recovered only after 20 days of treatment.

The frequency of improved unchanged or increased changes in the roentgenograms is shown in Table V There is no significant dif

Table V *Follow up examination Changes in roentgenograms*

Parentheses denote confidence limits. $P = 0.05$

	Pivampicillin-treated group (no. of sinuses)	Control group (no. of sinuses)
Improved	39 61 9% (48.8–73.9 %)	60 75 9 (65.0–84.9)
Unchanged	16 25 4 % (15.3–37 9)	13 16.5 (9.0–.6.5)
Worse	8 1..7% (5 7–23.5)	6 7 6% (2.8–15.8)
	63	*79*

Table VI *Side effects*

Parentheses denote confidence limits. P 0 05

	Pivampicillin-treated group (no. of patients)	Control group (no of patients)
Nausea	0	
Vomiting	0	1
Abdominal pain	4	0
Urticaria	1	1
Diarrhoea (loose stools)	1	1
GP-transaminase elevated	1	4
Discontinuation necessary	3 6 8 (1 4–18 7)	1 1 9 (0 1 10 1)

ference as far as this concerns either ($p > 0.05$) In only 2 cases in the pivampicillin treated group and in one in the control group with increasing changes did the symptoms recur Secretion from the sinuses and other symptoms seem to disappear earlier than the changes in the mucosa, as demonstrated by X-ray

Side effects

The frequency of the various side effects in the two groups is shown in Table VI. The treatment had to be discontinued in 3 patients in the pivampicillin-treated group (6.8% of the group) however it was also necessary in 1 patient in the control group (1.9% of the group) as the patient developed severe urticaria, nausea and diarrhoea. The difference found is not significant ($p > 0.05$) In all cases the interruption took place after cessation of secretion. In 1 of the 3 cases in the pivampicillin-treated group, the complaints had recurred by the time follow up examination was carried out, possibly due to the interruption in the treatment. No other side effects were observed.

DISCUSSION

The average recovery time in both groups is shorter than that often found in the literature (Kortekangas, 1963 Reynolds et al. 1964 Jeppesen & Schaldemose, 1970) This could possibly be explained by the fact that all patients in this material were treated with daily lavage in contrast to two to three times weekly often chosen in previous investigations. The frequency of cases in which bacteria were demonstrated in the secretion is also lower than in the literature (Kortekangas 1963 Lystad et al., 1963 Reynolds et al., 1964 Jeppesen & Schaldemose 1970). This could possibly be explained by the fact that antibiotic treatment was often given by general practitioners prior to the patient s referral to our department. However an analysis of the material with regard to earlier antibiotic treatment does not disclose a significantly lower frequency of bac

Table VII *Bacterial growth related to treatment with antibiotics prior to admission to the trial*

Parentheses denote confidence limits. P 0 05

	Pivampicillin treated group (no. of sinuses)	Control group (no of sinuses)	Total (no. of sinuses)
Antibiotic treatment given before			
No growth	5	10	15 57 7 (36 9 76 7)
Growth	4	7	*11*
Total	9 14.3 (6.8–.5 4)	17 1 5 (13 1 3.. .)	26
Antibiotic treatment not given before			
No growth	45	43	88 76 0% (67.. 83 4
Growth	9	19	25
Total	54	[illegible]	116
Total	*63*	*79*	*14*

terial growth from the secretions in these cases (Table VII). The material may then include a relatively large number of cases either recovering from bacterial sinusitis, which adds to the shorter recovery time mentioned above, or with mucosal changes and secretion of origins other than bacterial infection. Finally it could be explained by a failure of the bacteriological examination to demonstrate existing bacteria in some of the cases. The low frequency of bacteria could possibly explain the lack of effect of pivampicillin on the recovery time in this study. However no effect was found even in cases in which bacteria were demonstrated. These groups are too small for further analysis as regards M.I.C. values for the bacteria. Finally it should be remembered that the material does not include acute cases with fever. Within these limitations the result agrees with an earlier study as regards ampicillin in the treatment of sinusitis (Kortekangas, 1965).

Finally it should be noted that the recovery time is the only criterion used in this study. It does not exclude the possibility that the treatment could result in symptoms other than secretion, such as abatement of pain and fever at an earlier stage of the treatment or in some protection against complications in some cases, caused by sensitive bacteria.

CONCLUSION

It has not been possible to demonstrate any effect of pivampicillin (356 mg four times daily) on the recovery time from acute, subacute or chronic maxillary sinusitis in a series also treated with nasal decongestant and daily lavage. The possibility that a higher dosage may have some effect has not been studied. The number of cases in which bacteria were demonstrated was too small for further analysis with regard to the M.I.C. values for the bacteria. The series does not include acute cases with fever.

The treatment had to be discontinued in 3 patients in the pivampicillin-treated group as the patients developed urticaria, nausea or abdominal pain and diarrhoea. However discontinuance was also necessary in one patient in the control group due to the same side effects.

ACKNOWLEDGMENT

We wish to express our gratitude to Leo Pharmaceutical Products, Copenhagen, who provided the Pondocillin employed in the investigation.

ZUSAMMENFASSUNG

Systematische Behandlung mit Antibiotika scheint nur eine zweifelhafte oder geringe Wirkung auf die Heilung der Sinusitis Maxillaris zu haben. Da es festgestellt worden ist, dass man, nach Eingabe von einem neuen peroralen Ampicillinderivat, Pivampicillin (Pondocillin®) eine genügende Gewebekonzentration von Ampicillin erwarten kann, könnte man irgendeine Wirkung in der Behandlung einer von empfindlichen Bakterien verursachten Kieferhöhlenentzündung erwarten.

In einer doppelt blinden Untersuchung von den akuten, subakuten oder chronischen Fällen der eitrigen Kieferhöhlenentzündung wurden 45 Patienten viermal täglich mit Pivampicillin 356 mg, mit nasal detumeszierenden Nasentropfen, samt täglicher Spülung behandelt, und 55 Patienten wurden mit Placebo, detumeszierenden Nasentropfen und täglicher Spülung behandelt. Die Untersuchung offenbarte einen Unterschied in der Heilungszeit von 0,9 Tage. Dieser Unterschied ist nicht signifikant. Die Behandlung musste bei drei Patienten in der Pivampicillingruppe abgebrochen werden, da die Patienten Urticaria, Nausea oder Magenschmerzen und Diarrhoe bekamen. Indessen musste man bei einem der Patienten in der Kontrollgruppe, die Behandlung infolge derselben Nebenwirkungen abbrechen.

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DEVELOPMENT OF TONE BURST RESPONSES ALONG THE AUDITORY PATHWAY IN THE CAT

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Abstract. Microelectrodes were used to record responses evoked in the cochlear nuclei, inferior colliculus, and medial geniculate body to pure tone auditory stimulation at various stages after birth in young cats. Cortical evoked responses were recorded with the aid of macroelectrodes. The time of the earliest recordable responses to physiological stimulation does not reveal as valuable information about the maturation of the central auditory centers as such criteria as response latency fatigability changes in threshold, frequency spectrum, and evidence of inhibition. Our physiological results show that maturation of the auditory pathway proceeds centripetally in accordance with some histological data. According to preliminary data, the last stage of the auditory system to become functionally mature may be the hair cell nerve ending synapse because the cochlear microphonic can be elicited by sounds and the central auditory pathways electrically stimulated before the action potential responses can be recorded.

Most of the work done on the development of the auditory system in mammals is limited to the peripheral portion, i.e. the cochlea. Among the most important in the area of histology are the works of Retzius (1884) of Wada (1923), of Bast & Anson (1949) and more recently those of Kikuchi & Hilding (1965) and Ruben (1967). Others have studied the physiological relationships, while still staying at the cochlear level. Larsell et al. (1935 1944), Alford & Ruben (1963), Klyavma & Marusseva (1963) and Änggård (1965). The development of hearing in its central parts has, in fact, been approached by only a few authors such as Rose et al. (1957) and Marty (1962)

Previous experiments have shown that electrocortical responses to tonal stimulus in cats could be recorded in the very first days following birth (Pujol et al. 1966). We have correlated these first responses with the development of the organ of Corti (Pujol & Marty 1968, 1970) The purpose of this paper is to describe the sequence of appearance of various aspects of the auditory function in the kitten. Macrophysiological research at the level of the cortex and microphysiological research at the level of the relay nuclei was described in several brief notes (Pujol et al., 1968 1969 1970). These results will be incorporated in an effort to better synthesize an overall view of the important developmental steps.

MATERIAL AND METHODS

These experiments were performed on cats varying from newborn to adults, approximately 150 newborn 50 between 1 week and 2 months and 15 adults, under light sodium pentobarbital anesthesia. The stimulus generally used was a tone-burst emitted by a Hewlett-Packard oscillator (4204A) coupled with a Grason Stadler electronic switch (829C) The sound was emitted by monaural tra er a sealed tube attached to the exte

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meatus of the animal. The parameters of stimulation were the following: rise and decay time of 5 ms, frequencies between 150 and 15 000 Hz, intensity up to 90 dB at the reference level 0.0002 dyn/cm² on the ear drum, sound duration from 25 to 1 000 ms. Recording was done stereotactically at the level of cochlear nucleus (CN) essentially in its ventral part, inferior colliculus (IC) and medial geniculate body (MGB) by means of glass insulated platinum micro-electrodes (Wolbarsht et al., 1961) from 1 to 5 MΩ of impedance. At the level of the auditory cortex only monopolar or transcortical silver electrodes were used. Electrophysiological activities were amplified by a Grass (P 511) and a selective spike filter and stored on a Philips (A 7) analogical recorder. They were then either directly visualized on a Tektronix (561 A) oscilloscope, or previously processed on a Nuclear-Chicago computer (DRC 7102) permitting accurate evaluation of the latencies of the evoked potentials and establishment of PST histograms of unit activities. Stimulation and recording equipment was controlled and synchronized by an E.M.O. double impulsion stimulator.

A part of the data was processed statistically in order to establish the regression curves of the latencies at each of the stages of the auditory pathway. The form of scattering of points obtained led us to seek X to the power n regressions, but it was necessary to determine an origin for each of the curves. As the experiment showed that the simultaneity of the appearance of responses was attributable to a peripheral factor, i.e. the late delay in the development of the receptors, it was decided to adopt a more probable hypothesis postulating the successive origin of the responses at the different stages from the periphery to the cortex. The mathematical methods used were the following: a is the origin of the regression which may be located before birth, Yx is the average of Y (latency) for a given value of X (animal's age counted starting from a). It is possible to say, by way of hypothesis, that the regression Yx is not too different from a X^n regression and the best approximation of the curve is then a $Y = e^a X^b$ form hyperbola. The probability test is done by referring the correlation coefficient between Z (log Y) and T (log X) to a statistical F table (0.1% of probability level).

RESULTS

Evoked potentials (EP)

First responses. The first EP were obtained nearly simultaneously in the different parts of the auditory system in the very first days following birth. To obtain early responses it is necessary to use high intensity stimulation (close to 90 dB at the eardrum) and frequencies limited to a band between 250 and 2 500 Hz (tonal restriction). No significant variation of these stimulation requirements were noticed in terms of the place of recording. During the first week after birth, the threshold drops and the range of effective frequencies enlarge rapidly (Fig. 1). By age 10 days, responses were observed at all frequencies between 150 and 15 000 Hz.

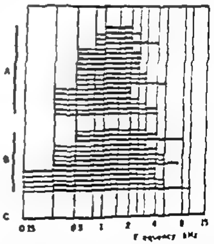

Fig. 1. Electrocortical responses to tonal stimulation in the kitten. Recordings were made on 18 litter... aged 2 or 3 days (A), 13 aged 5 or 6 days (B) and 8 aged 10 days (C): all responses in the last group were identical. Each horizontal line represents the range of effective frequencies in one animal. Thick and thin lines represent good and poor responses respectively.

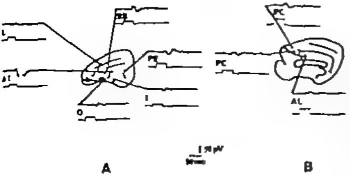

Fig 2 Electrocortical responses to tone-burst stimulation in a kitten aged 3 days. (*A*) Responses recorded on the lateral cortical areas: primary auditory cortex (*AI*), lateral gyrus (*L*), suprasylvian gyrus (*SS*), posterior ectosylvian area (*PE*), insular area (*I*) and orbital area (*O*). (*B*) Responses recorded on the medial cortical areas: peri-cruciatum gyrus (*PC*), anterior limbic area (*AL*). Each response represents the EP averaged over 25 responses. Stimulus: 1 500 Hz, 90 dB SPL, 50 ms.

The earliest recordable EP are already mature as far as their form and amplitude are concerned. This is very clear in particular in the first relay nuclei. In the IC the first EP may reach 500 μV and have a configuration of the adult type. The early cortical responses are less well developed, with an amplitude of 20 to 50 μV, however in the primary areas (AI and AII) EP are already formed by the positive and negative waves characteristic of adult potentials (at this stage a predominance of the negative wave is noticeable). Likewise, in this first stage it is possible to register EP either in the primary and extra primary territories as the pars medialis of the MGB or the orbital, insular suprasylvian and peri-crucial cortical areas (Fig. 2).

Evolution of latency The most distinct characteristic of the immaturity of the first EP is their long latency. At 2 or 3 days they are of the order of 12 ms (CN), 20 ms (IC), 30 ms (MGB) and 60 ms (AI). During the first weeks after birth we witness a regression of these values and the adult latencies, i.e. 3 ms (CN), 6 ms (IC), 7 to 8 ms (MGB) and 9 to 10 ms (AI) will be reached respectively by each of the levels of the auditory pathway from the

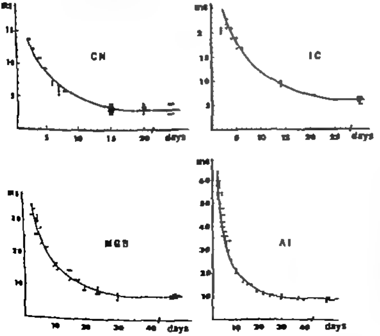

Fig 3 Postnatal evolution of the EP latencies in the auditory pathway of the cat. Responses recorded in cochlear nuclei (*CN*), inferior colliculus (*IC*), medial geniculate body (*MGB*) and primary auditory cortex (*AI*). The end of each regression is indicated by a dotted line.

periphery to the cerebral cortex. A statistical study of these regressions was done according to the method described previously. We arrive at the following equations reported on Fig. 3

$$\text{CN}\begin{cases} Y = 388\,(X+7)^{-1.\text{[illegible]}} & \text{when } -7 \leq X \leq 18 \\ Y = 3 & \text{when } X > 18 \end{cases}$$

$$\text{IC}\begin{cases} Y = 181\,(X+5)^{-1.\text{[illegible]}} & \text{when } -5 \leq X \leq 25 \\ Y = 6 & \text{when } X > 25 \end{cases}$$

$$\text{MGB}\begin{cases} Y = 141\,(X+2)^{-\text{[illegible]}} & \text{when } -2 \leq X \leq 32 \\ Y = 7.2 & \text{when } X > 32 \end{cases}$$

$$\text{AI}\begin{cases} Y = 117\,(X)^{-0.\text{[illegible]}} & \text{when } 0 \leq X \text{ or } X \leq 40 \\ Y = 9.4 & \text{when } X > 40 \end{cases}$$

Unit responses

The microphysiological experiments were limited in this work, to the 3 relays of the afferent auditory pathway and the number of units activated by tonal stimulation was [illegible] (72 in NC, 122 in IC, 66 in MGB).[1] O- factor of stimulation was particularly studied the duration of the stimulus. The differ- types of unit responses encountered and the postnatal evolution are hereby described.

On responses. This is the mode of reacting of all the early unit responses. At this early phase, as soon as the stimulus reached a sufficient level of intensity it provoked only a single burst of spikes, usually limited to 2 or (Fig. 4 *a*). Increasing the intensity and dura- *tion of the stimulus did* not affect this re- sponse.

Rhythmic responses. Starting at the end of the first postnatal week we noticed the evol- tion of a large number of on responses i the first 2 relay nuclei (CN and IC). In fa for long duration stimuli, we found an ini- *on burst with a latency shorter than previou* observed, but this on burst was now follow by new bursts at regular intervals of abo 100 ms (Fig. 4 *b*). During the second wee these intervals decreased regularly and th response became more continuous (Fig. 5). A the level of the MGB this type of developme was not as clear as in the more peripher sites studied. The first rhythmic responses we *not registered there until the third postna* week and only a small number of units we involved.

Continuous responses. From the fifteenth da in CN and a few days later in IC, the rhythm *responses were replaced by* responses of t continuous type. During protracted stim- tions the on burst, which was still noticeab on the histograms, was followed without in-

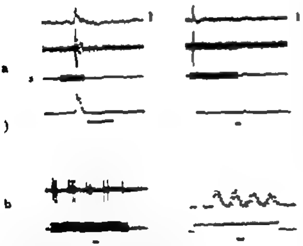

Fig. 4. First unit response to tone-burst stimulation. (*a*) "On" responses in IC of a -day-old kitten. EP (1), unit response ( ), stimulus (3), and PSTH of 50 responses (4) are represented. Unit responses are not affected by the duration of the stimulus 50 ms (left), 500 ms (right). Frequency: 1 500 Hz. (*b*) Rhythmic response in CN of a 7-day-old kitten. On the right PSTH of 50 responses from the same unit. Stimulus duration: 800 ms. Unit time: 50 ms. Frequency: 500 H.

[1] The exploration of the auditory cortex in kittens by means of microelectrodes has now been undertak and the preliminary results ha e just been p- (Konig, Pujol & Marty 1977)

ruption by continuous bursts of spikes even throughout stimuli lasting several seconds (Fig. 6). In MGB some continuous responses were recorded but only at the end of the first postnatal month.

Responses with inhibitory mechanisms These responses which were not frequent at the level of CN where most of the cells developed according to the schedule described above were found with increasing frequency as we advanced up the auditory pathway At the level of the IC, starting at the end of the first week, we registered a pattern of rhythmic responses where the first period of silence that followed the on burst was much longer than the others, or about 200 ms. In the following days, while the response developed towards a continuous type, the first silent period became shorter but did not disappear completely (Fig. 7 *a*). At the level of IC and even more at the MGB we also found, at the end of the developmental period, short latency responses of the on mode indicating very marked inhibitory mechanisms. At the level of the MGB many other types of responses with inhibition may be registered, at this time, such as responses with reverberation and off responses (Fig. 7 *b*).

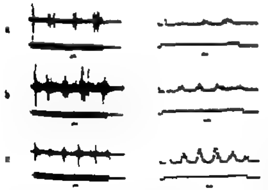

Fig. 5 Maturation of rhythmic responses in the inferior colliculus. Kittens aged 6 days (*a*), 8 days (*b*), and 10 days (*c*). The silent periods between bursts become shorter with increasing age Stimulus duration 600 ms. Unit time 50 ms. Frequency (all traces) 3 000 Hz.

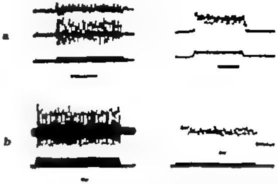

Fig 6 Continuous responses to tone-burst stimulation. CN unit of kitten aged 15 days (*a*) and IC unit of kitten aged 20 days (*b*). The "on" bursts are still noticeable on the PSTH of 50 responses (right). (*a*) Stimulus duration, 120 ms; frequency 1 500 Hz. (*b*) Stimulus, 800 ms; frequency 5 000. Unit time: 50 ms.

DISCUSSION

Evoked potentials

First responses. Previously by using clicks, Rose et al. (1957) then Ellingson & Wilcott (1960) and Marty (1962) obtained the earliest electrocortical responses between the 6th and

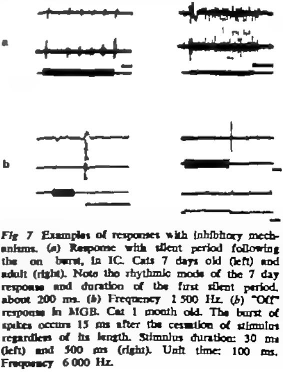

Fig 7 Examples of responses with inhibitory mechanisms. (*a*) Response with silent period following the on burst, in IC. Cats 7 days old (left) and adult (right). Note the rhythmic mode of the 7 day response and duration of the first silent period, about 200 ms. (*b*) Frequency 1 500 Hz. (*b*) "Off" response in MGB. Cat 1 month old. The burst of spikes occurs 15 ms after the cessation of stimulus regardless of its length. Stimulus duration: 30 ms (left) and 500 ms (right). Unit time: 100 ms. Frequency 6 000 Hz.

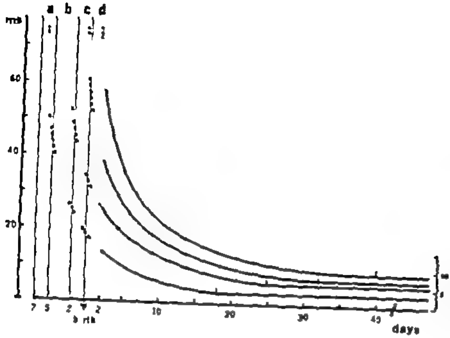

Fig. 8. Comparison of t[he] evolution of EP latenc[ies] in CN (*a*), IC (*b*), MGB (*c*) and auditory cort[ex] (*d*). The curves are ex-tended by dotted lines to their probable origin.

the 8th postnatal days. The importance of the means of stimulation was emphasized by the results of Änggård (1965) who obtained in the rabbit, at birth less mature than the cat, the first cochlear response to tone-burst at a relatively early date, i.e. 5th day. It is conceivable that in dogs comparable experiments would make it possible to record earlier responses than 12th or 14th postnatal days, a[s] observed in previous studies (Zahlavá, 196[6]; Fox, 1968). In the cat, the fact that the fir[st] responses were obtained simultaneously at a[ll] levels prevents establishment of a chronologica[l] sequence for functional maturation of vario[us] parts of the auditory system. Experiments con-ducted on the most peripheral portion (Ro-mand et al., 1970) have recently shown th[at] simultaneity is not the rule at that level. Th[e] cochlear microphonic was always present a[t] birth, but the eighth nerve action potentia[l] appeared often 1 day later. However th[e] nervous pathway in its entirety is also rea[dy] to function at birth as proved by its electric[al] stimulability (Marty & Thomas, 1963; Her-mannová & Myslivecek, 1965). The last phas[e] of the entry into function of the auditor[y] system may then take place at th[e] level o[f] the neuroepithelial synapses, and studies a[t] this level in the field of microphysiolo[gy] (Sohmer et al., 1971) or electron microsco[py] (Hilding, 1969) would be able to provide me[an]-ing information. It is also reasonable to ex-pect that a study now under way on electric stimulation in the prenatal period w[ill] permit the establishment of a more accura[te] chronology of the early events of functio[n]

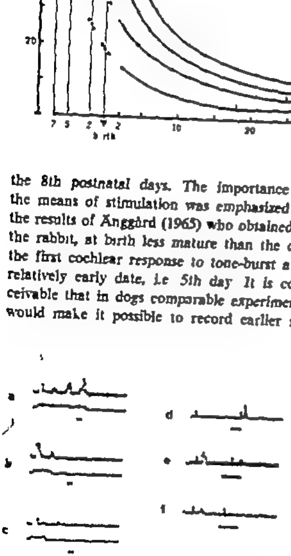

Fig. 9. Interpretation of the rhythmic response in the IC of -day-old kitten. On the left, rhythmic responses with a stimulus decreasing in duration from (*a*) to (*c*). Notice in (*c*) that a stimulus shorter than 100 ms generates only an "on" burst. On the right (*d* to *f*), the same unit is activated by two clicks of equal intensity. A second click emitted at less than 100 ms (*f*) did not provoke a second response. Unit time-50 ms. Frequency (*a*–*c*), .000 Hz.

development by defining, for example, a mesencephalic stage.

Evolution of the latencies. The study of the evolution of the EP latencies gives us a precise indication of the very distinctly corticopetal kinetics of the auditory pathway's development. The juxtaposition on one graph of the four regression curves, and the comparison of the dates of acquisition of definitive latency are very significant in this respect (Fig. 8) These results agree temporally with the centripetal process of myelination of the auditory pathway as described by Tilney & Casamajor (1924).

Unit responses

The earliest unit responses recorded at all levels is the "on" reactivity This is difficult to compare with the "on" responses previously described in the adult animal since these responses are the intervention of marked inhibitory mechanisms (Gerstein et al., 1968) This type of response in young animals probably indicates the immaturity of neurons which can only respond by a one spike burst even with the long duration stimuli. During the first weeks of postnatal life an important part of these responses is evolving. In particular this present series of experiments has shown one stage of the development, the rhythmic responses, which are very frequent in the CN and IC between the 7th and 15th days. In the CN of adult animals, Pfeiffer (1966) has described a chopper mode of discharges, but the intervals between the different peaks are very short (about 5 ms) and this mode is only noticeable in brief PST histograms. In the maturing auditory system the long silent periods which interrupt the bursts of spikes seems due to the peculiar fatigability of neurons as indicated by two kinds of arguments. First, there are transitory stages between the rhythmic and the continuous responses (Fig 5). The second argument involves a study of reactions to click stimulation. If we stimulated a rhythmic unit, not with a tone burst, but by means of two clicks of equal intensity the two had to be separated by an interval corresponding to the silent periods. With shorter intervals a second response was not obtained (Fig. 9)

The maturation of the various responses in which inhibitory mechanisms interfere is in accord with observations previously made in adult animals (Rose et al., 1963 Gerstein & Kiang, 1964). They indicate the increasing importance of these mechanisms in the auditory pathway as the cerebral cortex is approached. In the adult animal, one may think that cortical efferents play an important role in the organization of these responses (Watanabe et al., 1966 Amato et al., 1969). If these explanations are to be applied to the newborn, one must recall that certain responses, such as the response with silent period at IC appear very early at an age in which it is difficult to talk of organized cortical efferents. It is therefore more rewarding, at that stage, to interpret these inhibitory mechanisms in terms of local post-synaptic interactions (Nelson & Erulkar 1963)

The centripetal process of the development of the auditory system which came out clearly from the study of evoked potential is also confirmed by the unit recording. They even show a very clear time-lag between the early maturation of the first relays (CN and IC) and the later one of the MGB We can probably recognize here the ontogenetic expression of a phylogenetically important mesencephalic state

In conclusion, this work permits one to establish that the physiological maturation of the different portions of the auditory system is not simultaneous but proceeds stage by stage from the periphery to the cerebral cortex. The acquisition of the auditory function, in the cat, occurs gradually during the first weeks after birth and it is possible to distinguish several phases. Responses to tonal stimulation appear during the first postnatal days, but hearing is very limited, high threshold, tonal restriction, long latency of the responses and

lack of duration coding Between the 15th and 20th days we observe a clear improvement which coincides on the one hand with the completion of cochlear maturation and on the other with the rapid maturation of CN and IC, thresholds are lowered considerably there is no longer tonal restriction and the duration of the sound is perceived (continuous responses) Finally it is only during the second month after birth that the adult auditory characteristics are acquired, definitive threshold, short latency of response and complex coding revealed by the presence of numerous inhibitory mechanisms in the unit reactivity of the higher levels.

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RÉSUMÉ

La maturation des réponses a la stimulation tonale a été étudiée chez le chat, dans la période postnatale Les enregistrements ont été effectués au niveau du cortex cérébral, à l'aide de macroélectrodes et, à celui des relais sous corticaux (noyaux cochléaires, colliculus inférieur et corps genouillé médian) à l'aide de microélectrodes. La maturation successive des différents étages de la voie auditive, depuis la périphérie jusqu'au cortex cérébral est révélée par l'étude de l'évolution des latences des potentiels évoqués et confirmée par celle du developpement des réponses unitaires. Le fait que les premières réponses apparaissent simultanément à tous les étages envisagés et la référence a des travaux antérieurs permettent de situer la dernière étape de l'entrée en fonction du système auditif au niveau des synapses neuro-épithéliales.

ZUSAMENFASSUNG

Untersucht wurde die postnatale Entwicklung der Antworten auf tonale Reizung bei der Katze Die kortikalen Antworten wurden mit Makro-Elektroden aufgenommen, während die Antworten in den subkortikalen Zentren (nucleus cochlearis colliculus inferior und corpus geniculatum medianum) mit Hilfe von Mikro-Elektroden registriert wurden. Die schrittweise Reifung der verschiedenen Stufen des auditiven Systems von der Peripherie bis zum Kortex wird an Hand der Entwicklung der Latenzen der evozierten Potentiale aufgezeigt. Dieses Ergebnis wird bestätigt durch die Resultate bezüglich der Entwicklung der zellulären Antworten. Die Tatsache, dass die ersten Antworten gleichzeitig auf allen Stufen des auditiven Systems erscheinen, lässt im Lichte einiger Ergebnisse früherer Untersuchungen darauf schliessen, dass es letztlich die Reifung der epithelio-neuronalen Synapsen ist, welche dieses System funktionsfähig werden lässt

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EXPERIMENTAL ACOUSTIC TRAUMA PART I

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Abstract Guinea pigs were overstimulated by noise with an intensity of 150 dB. In all animals there were total defects of the organ of Corti and the tympanic mesothelium and thus the basilar membrane became quite bare. On all Reissner's and basilar membranes there were typical perforations. The basilar membrane is perforated only in one direction which is considered to be a manifestation of the mechanical possibilities of the membrane when vibrated. Both membranes are almost equally resistant to the mechanical force of acoustic trauma.

Extremely intense noise the kinetic energy of which exceeds the mechanical cohesion of tissue has a destructive effect on the membranous cochlea. In addition to destruction of the sensory papilla and mesothelium from the tympanic wall of the basilar membrane ruptures of Reissner's and basilar membrane were observed. After acoustic overstimulation with an intensity of about 140 dB Davis et al. (1953) revealed destruction of the cells of the organ of Corti and the mesothelial tympanic layer of the basilar membrane Lawrence & Yantis (1957), Miller et al. (1963) and Pronin et al. (1972) also observed rupture of Reissner's membrane while they considered perforation of the basilar membrane as artefacts associated with the sectioning technique Similar findings were reported by Eldridge et al. (1957) and Covell (1953) Beagley (1965) found inconstant ruptures between Deiters and Hensen's cells. Spoendlin (1971) studied the relationship of changes in the ultrastructure of the organ of Corti and the duration and intensity of acoustic overstimulation

This report describes the manifestation of mechanical damage of the structures of the inner ear by extreme noise

MATERIAL AND METHODS

Guinea pigs of about 350 g body weight were placed singly into a net chamber with the head beneath the centre of pressure loud speaker coupled to a 300 W amplifier For stimulation a noise was used with an almost continuous spectrum and a flat maximum from 1 to 2 kHz for 6 min At the guinea pig head an intensity of 150 dB was recorded Immediately after stimulation the animals were sacrificed, both temporal bones were removed and the bullae were opened. The examination was always made first under a stereomicroscope *in situ* to observe all sites and the extent of pathological manifestation. Only the were isolated surface specimens evaluated in detail under a light microscope

The middle ears were examined in total of 30 animals. For detailed evaluation the surface specimens of 37 ears were assembled. Another 10 guinea pigs were used for auxiliary examinations and for the histological investigation of series of sections after embedding in paraffin.

RESULTS

Only in one eardrum of sixty was there a ... like rupture otherwise the middle ear ...

Fig. 1 Surface specimen of bare basilar membrane [illegible]wards: limbus spiralis, habenulae, perforatae, [illegible] capillaries. Above: remnants of bases of Hensen's cells with heavy contours. Haematoxylin.

cluding the ossicles did not display any traumatic changes. In all animals, complete loss of the organ of Corti was found in the second turn (Fig. 1) On the margins of the organ of Corti there were cracks dividing the organ into strips of cells which, separated *en masse* from the basilar membrane (Fig. 2) floated freely in the cochlear duct and were connected with the original structures only by one end. These strips were more than 2 mm long. Most frequently the strips of Hensen's cells and outer hair cells as well as a thin strip of lining cells were found on the side medial to the inner hair cells. At some sites of the decellularized total defect, the cell bases remained on the basilar membrane and form thus a mosaic of typical patterns.

In all animals there were round or oval perforations of Reissner's membrane. The length of oval perforations along the spiral axis of the cochlea varied, the maximum being 3 mm. The edges were always smooth with the thicker rim and were never torn to pieces

Fig. 2. Edge of the defect of the organ of Corti. Longitudinal fissures divide the sensory papilla into strips of cells separated en masse. SS epithelium of sulcus spir. ext., PC pillar cells, HDC outer Deiters cells, HC Hensen's cells. Surface

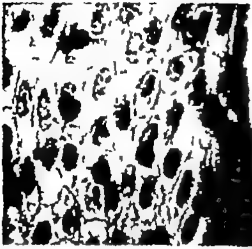

Fig 3 Edge of perforation of Reissner's membrane Haematoxylin.

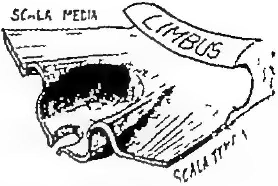

Fig 5 Perforated hernia of basilar membrane. Seen diagrammatically according to stereomicroscopic appearance.

as happens during damage with an instrument during perforation (Fig. 3)

In all animals there were typical perforations of basilar membrane which always affected the peripheral zone alone—pars pectinata (Fig 4) From the varying extent of the damage it is possible to obtain an idea of the development of the rupture and summarize it as follows: Diastasis of upper layer of the membrane – fragmentation of bundles of fibres – distension of the lower layer of the membrane – herniation – secondary diverticulum and its perforation. The similarity with hernia is so striking that we consider this term most pertinent (Fig 5).

In diastasis of the upper layer of the membrane the fission is radial and the edges look like folded rims of a subtle membrane. The remaining portion of the basilar membrane prolapses. Subsequently the bundles of fibrils in the lower layer of the membrane break and form fragments of varying length (Fig 6) The firmness of the membrane is breached and the prolapse increases like a hernia Between the thin and torn bundles of fibrils another diverticulum then appears as a secondary diverticulum which finally perforates (Fig 7). The largest hernia in our observation was 230 μ in size and the largest perforation had a diameter 70 μ. Near the perforation the spiral capillary is usually torn (Fig 4) and blood cells escape from it. We

Fig 4 Surface specimen of ... ... basilar membrane ... hernia Spiral capillary is ...

Fig 6 Fragmentation of bundles of fibres of basilar membrane Surface specimen. (*A*) Obj 40, Oc 10. (*B*) Obj 100, Oc 10.

d not find any other morphological forms suggesting damage of the integrity of the basilar membrane

The extent of total defect of the organ of Corti, and the distribution and frequency of the perforations of the basilar and Reissner's membrane are illustrated in the diagram (Fig. 8). The variability of the site of damage not only among individual animals but also between the ears of the same animal is apparent from the diagram. This variability was discussed by Stockwell et al. (1969) and by Spoendlin (1971)

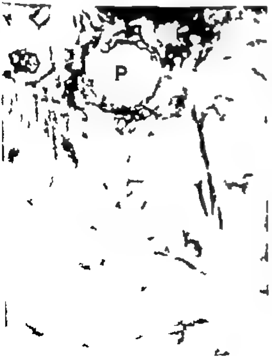

Fig. 7 Perforation (*P*) at the base of hernia of basilar membrane. Surface specimen.

DISCUSSION

Beagley (1965) described fissures in the junction of Deiters and Hensen's cells after stimulation with 128 dB. In our material after over stimulation with higher intensity the fissures were much larger and destroyed the whole organ. The cords of cells strips were all turned away from the total defect in the direction of the vortices which were observed by Békésy (1953) Moreover we also consider remnants of cell bases on the basilar membrane as a marked manifestation of mechanical injury (Fig. 1) Such remnants of cell bases are not found in any stage in the necrotic organ of Corti damaged by e.g., ototoxic antibiotics.

Perforation of Reissner's and basilar membrane are found in section where there is a total defect of the organ of Corti. The different appearance of ruptures of membranes can be explained by their different structure. In the basilar membrane the ground contains radial fibrils. In the medial

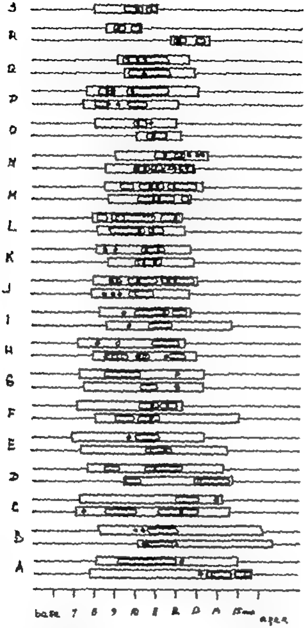

Fig. 8. Extend and site of total defects, perforations of basilar and Reissner's membrane. Capital letter: experimental animals, the lower column the left ear and the upper column the right ear. Ordinate: distance from the base of the cochlea in mm. Blank field: total defect of organ of Corti. O- perforation of basilar membrane. ○ perforation of Reissner's membrane.

(pars tecta) the system of fibres is uniform in the lateral zone (pars pectinata) it is divided into two layers. The upper one close beneath the surface of the membrane upon which Corti's organ is planted, consists of thin bundles of fibrils which lie close to each other and which anastomize with each other. The lower layer is formed by thick bundles which take an arc-shaped course with the convexity into the scala tympani (Engström, 1955; Iurato, 1962). From the observations mentioned above we conclude that the fibrils of the membrane cannot be prolonged, or only very slightly even when they are not stressed. Thus only a small deviation of the membrane is possible whereby it can divert relatively more into the scala media than into the scala tympani because the arc-like course of the lower layer of fibrils limits the excursion especially in the direction to the scala tympani. If the multiple is greater than the mechanical strength of the membrane and the energy is sufficiently strong, the inelastic reinforcement is failed by tension and the non-contractible fibres are torn into fragments (Fig. 6). Thus first the upper layer breaks, the fibres of which, due to their almost straight course, have only a small reserve as regards length. Then the relatively longer bundles of best fibrils of the lower layer break. The slacker ground substance of the membrane prolapses till its mechanical cohesion is impaired and it becomes perforated. The possibility of smaller deviations of the basilar membrane in the direction towards the scala tympani might explain the orientation of hernias and perforation in the same direction. There is, however, also the reflection on the non-linear distortion of vibrations during high intensities when the excursion of the stapes in the direction towards the inner ear was smaller than the opposite deviation.

The site of perforation of the basilar membrane in the radial direction is always at the junction of Deiters and Hensen's cells. At that site the first cracks on the surface of the organ of Corti also appear. Hoshino & Paparella (1970) observed on the basilar membrane herniations into scala tympani at the junction Hensen–Claudius in cases with experimental hydrops.

In addition to the traumatic changes de-

ribed there were in all examined ears marked gns of cell damage as is also known from numerous publications where lower intensities f noise were used which are considered the nsequence of metabolic exhaustion of cells. o this must be added the secondary changes used by mixing of the inner ear fluids as roved by Duvall and his collaborators (Duvall Rhodes, 1967 Duvall et al. 1969) and by oldstein & Mizukoshi (1967) *in vitro*

ZUSAMMENFASSUNG

Gruppe von Meerschweinchen wurde durch lerlusch von einer Intensität von 150 dB belastet. allen Meerschweinchen kamen grosse Totaldefekte Cortischen Organes und des tympanalen mesolen Epithels vor so dass die Basilarmembrane nz entblösst wurde. Auf allen Reissner und Basilar mbranen waren die charakteristischen Perforation, deren morphologisches Aussehen von der Strukanordnung der Membrane abhängig ist. Die Basilar bane ist nur in einer Richtung perforiert und les wird als Ausdruck der mechanischen Möglichkeit der Membrane bei Vibrationen angesehen. Beide Membranen sind fast gleich gegen die mechanische walt des akustischen Traumas widerstandsfähig.

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TEMPORAL INTEGRATION OF ACOUSTIC ENERGY IN NORMAL HEARING PERSONS

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Abstract. The relation between stimulus duration and stimulus intensity in perception of acoustic energy generally referred to as the temporal integration, i.e. temporal summation is investigated. In previous studies a wide variety of methods has been used, and accordingly different results have been obtained. To establish a normal material for later comparison of temporal integration in hearing impaired ears 30 normal persons were investigated. Temporal integration was measured as monaural threshold determinations for the frequencies 500, 1 kHz, 2 kHz, 4 kHz, and 8 kHz using stimulus durations varying from 1 to 1 000 msec. The results show that when halving the stimulus duration the sound pressure must be increased 3 dB to maintain the threshold, thus keeping the acoustic energy constant. A clear frequency dependence in temporal integration is demonstrated. We hope that the method of calculating temporal integration in this trial will facilitate the comparison of results of different investigators and thereby extend use of temporal integration measurements as an tool.

The relation between stimulus duration and stimulus intensity in perception of acoustic energy is generally referred to as the temporal integration = temporal summation. Temporal integration of acoustic energy describes the increased sound impression, which is achieved by increasing stimulus duration, keeping the sound pressure constant. Changes in the temporal integration or perception of short tones have been considered as one of the reasons for reduced discrimination in hearing impaired ears. Hinchcliffe (1970) and Broadbent & Stephens (1970) have called for investigation of short tone perception in hearing impaired ears.

To be able to compare the temporal integration in hearing impaired ears with normal ears, the literature was examined. It soon became evident that differences of opinions existed on several points. The temporal integration of acoustic energy is usually studied at threshold or at a masked threshold by determining the stimulus intensity necessary for threshold responses, while stimulus duration is varied. In measurements of temporal integration a well defined pulse-duration and shape is important. Rise and decay times used in previous studies do vary considerably Garner & Miller (1947) used 10 msec rise–decay time. Bentzen (1953) Goldstein & Kramer (1960), Zwicker & Wright (1963) Olsen & Carhart (1966), Watson & Gengel (1969), and Martin & Wofford (1970) also used relatively long rise–decay times varying from 4 to 10 msec. In the early work of Hughes (1946) a rise–decay time less than 1 msec was used. Eisenberg (1956), Jerger (1955) Green et al. (1956), Sheeley & Bilger (1964), and Thurlow & Bowman (1957) also used rise–decay times less than 1 msec.

Furthermore differences in the manner of defining the signal duration and the use of filters in the acoustic equipment increase the variety of experimental conditions.

The numbers of persons investigated in different trials are the following: Goldstein & Kramer (1960) investigated 48 persons. Hattler & Northern (1970) 20 persons, and Olsen &

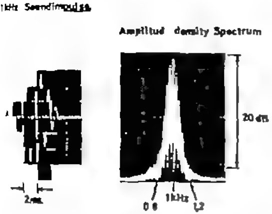


Fig. 1 Characteristics of a 1 kHz sound impulse, measured in a 3-chamber-artificial ear (Bruel & Kjaer 153). The figure serves to illustrate the frequency spread in the impulse with the relatively shortest rise-decay time.

Carhart (1966) 32 persons. Hughes (1946) and Plomp & Bouman (1959) based their measurements *on only 2 persons.*

Considering the differences in stimulus duration, rise-decay times, and testing procedures used, it is not surprising that measurements of temporal integration vary greatly and are difficult to compare.

A threshold shift of 3 dB by halving the stimulus duration within certain limits of duration would produce a perfect integration of acoustic energy Garner & Miller (1947), Hughes (1946) Goldstein & Kramer (1960) Plomp & Bouman (1959), Olsen & Carhart (1966), Sanders & Honig (1967), Martin & Wofford (1970) *did find this in their investigations.* On the other hand Green et al. (1956) and Broadbent & Stephens (1970) demonstrated a perfect integration within narrower limits of impulse duration. Finally an imperfect integration is described by Miskolczy Fodor (1953) Eisenberg (1956), Watson & Gengel (1969) Hattler & Northern (1970)

In the question of differences in temporal integration dependent of the stimulus frequency Bentzen (1953) Sheeley & Bilger (1964), Plomp & Bouman (1959) Eisenberg (1956), Hattler & Northern (1970) Martin & Wofford (1970) observed a frequency effect, while Zwicker & Wright (1963) and Olsen & Carhart *(1966) did not find this.*

From the literature we conclude that investigations of temporal integration in normal ears have been based on different methods *and accordingly different* results have been obtained. Therefore we found it necessary to establish our own normal material to be able to compare the temporal integration in hearing impaired ears with temporal integration in normal ears.

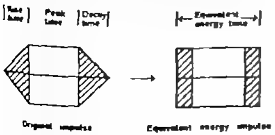


Fig. 2. Method for calculation of equivalent energy time. For explanation see text.

MATERIAL AND METHODS

In these investigations we used otologically normal persons with no history of ear diseases, head trauma or acoustic trauma with ages ranging between 10 and 30 years. The persons were investigated with conventional pure tone audiometry and to ensure an optimal selection and to avoid acoustic trauma the following requirements were made to the pure tone threshold regarding the five frequencies 500, 1 kHz, 2 kHz, 4 kHz, and 8 kHz:

1) The difference between highest and lowest value must not exceed 15 dB
2) the average value for the threshold for the five frequencies must not exceed 2.5 dB HL,
3) If the threshold at 4 kHz exceeds the values *at 1 kHz or 8 kHz it must not* exceed 2.5 dB HL.

The temporal integration was investigated with monaural threshold determinations

sound impulses of the frequencies 500 1 kHz, 2 kHz, 4 kHz, and 8 kHz.

The sound impulses are generated in a digital controlled sinus generator Salomon & Elberling (1968) equipped with a power amplifier and a 2.5 dB step attenuator The acoustic energy [illegible] delivered to the test persons through a conventional TDH-39 ear-phone.

The sound impulses have the following parameters. frequency amplitude, and duration which can be controlled separately The amplitude is calibrated in dB HL.

To ensure well defined and short sound impulses in the frequency as well as in the time domain we must determine the correlation between the frequency distribution and the rise- and decay-time This is done by minimizing the rise and decay time observing the frequency spread thus produced. The rise and decay of the tone pulses are linear and consist of an even number of periods of the base frequency The rise and decay-times selected in this trial constitute a compromise between. the ability to produce short sound impulses, to have a narrow frequency-band, and the available equipment (Fig. 1) The rise time as well as the decay-time used are the following: 500 Hz 4 msec, 1 000 Hz 2 msec, 2 000 Hz 3 msec, 4 000 Hz 3.5 msec, 8 000 Hz 1 75 msec.

An impulse is graphically demonstrated in Fig. 2. The impulse consists of rise-time peak and decay time. The peak time can be selected from 1 msec to 1 000 msec using the steps 1 2, and 5 By calculating the acoustic energy in rise and decay time this energy can be added to the acoustic energy in the peak time, thus producing an equivalent energy sound impulse, the amplitude of which is unchanged and with a duration called *equivalent energy time* (Fig. 2) This calculated energy time [illegible] used as the relevant expression of the stimulus duration. The equivalent energy times of the rise and the decay-times are the following: 500 Hz 4 7 msec, 1 000 Hz 2.3 msec, 2 000 Hz 2.5 msec, 4 000 Hz 2.6 msec, 8 000 Hz 1.3 msec.

Fig. 3 which demonstrates the results from a normal person illustrates our method [illegible] calculate the temporal integration. The results are graphically represented in a double logarithmic co-ordinate system. The abscissa is the logarithm to the equivalent energy time of the stimulus, and the ordinate is the threshold shift in dB relative to the "mean" threshold for long stimulus. According to Bentzen (1953) the "mean" threshold for long stimulus is calculated as a mean-value of the results obtained at 200 500, and 1 000 msec. The threshold shift for different impulse durations is shown. The points are fitted by a straight line calculated by the method of least squares. The shortest stimulus time giving a threshold equal to that obtained from long stimulus time is the point of initiation in calculating the straight line. The straight line has a slope called [illegible] dB/decade and cuts the ordinate axis in a point called A dB

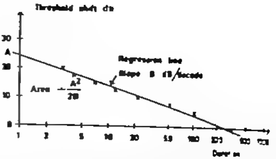


Fig 3 Record from a test person. The measured thresholds [illegible] 1 000 Hz, for 10 different stimulus durations. The figure serves to illustrate our method [illegible] calculate the relevant expressions A, B, and $-(A^2/2B)$ for the temporal integration, see text.

The area of the triangle formed by the abscissa axis, the ordinate axis, and the straight line is used to express the temporal integration. The area can be calculated with the knowledge of the A value and the B-value using the formula $-(A^2/2B)$.

Before each trial the subjects are informed about the nature of the test. They are told about the condition in a sound-proof room [illegible] well as the problems of disturbances from respiration and pulse sensation, especially at short stimulus durations. At each threshold determination the investigation starts [illegible] a sensa-

.e I. *Mean and standard deviation values for B and $-(A^2/2B)$ at five frequencies See text*

	Frequency (Hz) 500	1 000	2 000	4 000	8 000
M	26 6	26.0	24 1	22.3	20.8
S D.	3.6	4.9	3 0	2.8	3.0
M	−11.1	−10 8	−10.2	−9.1	−8 7
S D.	1.6	.1	1.8	1.2	1 4
(A ,2B)					
M	32.0	31 4	28.9	27.5	4.9
S D	4 9	6.5	4 5	4.3	3.8
	N = 30	N = 30	N = 10	N = 30	N = 30

level of 10–15 dB from where the intensity lowered in 2.5 dB steps.

The first part of the statistical computations consists of determining the above-mentioned values of A, B and $-(A^2/2B)$ our measure of temporal integration and investigations of the distributions for each frequency

The second part of the statistical analysis is a systematic attempt to describe the relationship between thresholdshift and the logarithm of the calculated energy time by a linear model i.e. the straight line computed by the method of least squares. For each of the five frequencies a series of individual regression lines is calculated, and the deviations between points and line are investigated with respect to sign and magnitude. The usual procedure for testing the identity of the individual regression lines is not applicable here—the mean and variance of the independent variable (time) being constant. Instead, all data for a given frequency are pooled and subjected to a conventional linear regression analysis with 30 observations of the threshold shift for each of the eight predetermined durations. (At 2 000 Hz only 10 persons were investigated.)

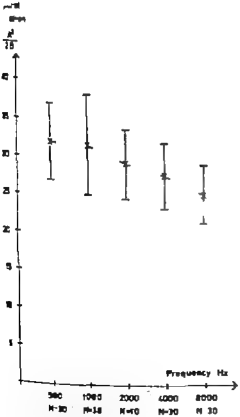


Fig. 4 Mean and standard deviation values for (A 2B) at five frequencies. Values from Table I, see text.

RESULTS

1) *Main results*, the analysis of the distribution of measures of A, B, $-(A^2/2B)$, calculated by the individual regression lines are summarized in Table I and illustrated in Fig. 4 For the

Table II *Pooled analysis of threshold shift determinations (dB) for each frequency and impulse duration*

Hz		Duration (peak time) (msec) 1	2	5	10	20	50	100	200
500	M	19 4	18.1	15.0	12.7	10.3	7.2	4.4	1 7
	S.D.	2.4	.4	2.7	2.8	2.6	1 7	1.9	1.5
1 000	M	21.6	19.3	16.4	13.3	10.3	7.6	4.5	1.8
	S.D	3.7	3.9	3.8	3 0	2.8	2.9	2.2	1.3
2 000	M	19.5	18 0	14 7	11.8	9.5	6.6	4 0	2.2
	S.D	.3	2.3	2.4	2.4	.3	2.6	2.7	0.9
4 000	M	18.1	16.5	14.0	11 4	9.3	7.0	4.4	1 7
	S.D	2.3	2.5	2.2	2.1	1.9	1.9	2.2	1 4
8 000	M	18 4	16.2	13.5	11.0	9.0	6 0	3 4	1.2
	S.D	2.6	2.6	2.4	[illegible]	2.0	1.8	1 7	1 4

Table III *Statistical information for the investigation of systematic deviation of the threshold shift (in dB) from individual regression lines at 500 H The confidence limits indicate the 95% fractiles. See text*

	Duration (peak time) (msec) 500 Hz $N=30$							
	1	2	5	10	20	50	100	200
Average deviations from individ. regression lines	1 198	0.631	−0.646	−0.972	−0.887	−0.149	0.227	0.597
Variance of deviations from individ. regression lines	0.863	0.814	0.767	1.570	1.558	1.073	1.300	1 061
Confidence								
Upper limit	+1.585	+1.018	−0.259	−0.585	−0.500	+0.241	+0 614	+0.984
Lower limit	+0.811	+0.244	−1 033	−1.359	−1.274	−0.533	−0.160	+0.210

frequency 500 Hz, 1 kHz, 4 kHz, and 8 kHz, the number of investigated persons (N) are 30 for 2 kHz $N=10$

2) The pooled analysis for each *impulse duration* is given in Table II and illustrated for 500 Hz in Fig. 5 which shows means and standard deviation threshold shifts for the eight values of the durations.

3) To investigate *systematic deviations* between measured points and calculated regression line, results from the individual analysis for 500 Hz are given.

The results are given in Table III and demonstrated in Fig. 6 The average deviation of observations from the individual regression lines is shown in the first line. The variance of these deviations is as follows. The pooled

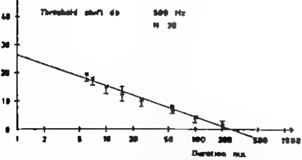


Fig 5 Pooled analysis of threshold determinations at 500 Hz for each impulse durations. Standard deviations indicated. Values from Table II.

estimate of the variance $=s^2$ is 1 1245 as $s=1\ 060$

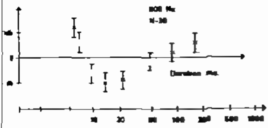
Confidence limits for average deviations at each duration can be calculated as average deviation $\pm 2(s/\sqrt{N})=\bar{x}\pm 0.387$ These confidence limits are presented also in Table III. Only two of the eight intervals contain zero.

Thus it is demonstrated that no linear relationship exists between the threshold shift and the impulse duration (see Discussion).

4) *The influence of the rise- and decay time* was investigated by using long and short rise-decay times. In 5 normal persons we measured the threshold-shift at 1 kHz using 14 msec as well as 2 msec rise-time for each individual and for the two different rise-times we calculated the A and B-value. The values for the long (14 msec) as well as for the short (2 msec) rise-time were pooled separately

Table IV *Mean value of A B and* $-(A/2B)$ *for five normal persons investigated with long* (14 msec) *and short* (2 msec) *rise time*

	Rise time (msec)	
1000 Hz $N=5$	14	2
A	23	25
B	−10	−11
−(A /2B)	26	23



;. 4 Average deviations from individual regression ies with indicated confidence limits (95% fractile) 500 Hz. Values from Table III, see text.

verage values were calculated, and the results re shown in Table IV

5) *Order effects.* To avoid order effects 19 ormal persons were investigated using the st frequencies in the sequence 500 1 kHz, kHz, and 8 kHz, and 11 persons were in- estigated using the sequence 4 kHz, 8 kHz, 00 Hz, and 1 kHz.

The calculations were performed as men- ioned above and the results are shown in Table V. They demonstrate that no order ffect is present.

DISCUSSION

Temporal integration of acoustic energy is con idered important in discrimination and can be measured by short tone audiometry. The re ults presented above constitute our normal material for temporal integration, produced

Table V. *Order effect values of A and B in two groups of normal persons with different test sequences*

19 normals		
Test sequence 500, 1000, 4000, 8000 Hz		
500 Hz	A = 26	B = −11
1000 Hz	A = 26	B = −11
4000 Hz	A = 22	B = − 9
8000 Hz	A = 21	B = − 9
11 normals		
Test sequence 4000, 8000, 500, 1000 Hz		
500 Hz	A = 27	B = −11
1000 Hz	A = 23	B = −10
4000 Hz	A = 21	B = − 9
8000 Hz	A = 19	B = − 8

for later comparison with temporal integration in hearing impaired ears. The results from 30 normal persons show that for stimulus duration below 200 msec the amplitude of the stimulus must be increased about 3 dB when time is halved. Similar results have been obtained by several investigators as mentioned in the introduction.

The temporal integration is found to be different for different frequencies, as demonstrated in Tables I and II and illustrated in Fig. 4. The steepest integration slope is found at 500 Hz, the flattest at 8 kHz. From the introduction it is seen that most investigators in this subject have observed a frequency effect on temporal integration. So far no explanation of this frequency effect has been given.

A systematic deviation of the measured points from the regression line is observed. The deviations at short durations have been explained by Garner (1947) as energy spread outside a critical band-width. The deviations from the regression line for longer durations have been explained by Plomp & Bouman (1959) and Zwislocki (1960). In their mathematical models a time constant referring to an exponential decay of the excitation in the acoustic system is the essential part. Although the deviation of the measured points from the individual regression line is systematic, the error in expressing the temporal integration by a regression line is negligibly small.

The influence of rise–decay time is investigated. Wright (1967) recommended a rise–decay time at 10 msec duration in clinical use. Dallos & Johnson (1966) investigated the influence of rise–decay time in the area from 0–40 msec. They showed that as long as the equivalent energy impulse duration was unchanged, the rise–decay time had no effect upon the auditory threshold. Our investigations confirm that equal results are obtained using either long or short rise–decay times, when the rise–decay time is calculated and included in the equivalent energy time.

Finally the investigation demonstrates that no order effect is present.

In the introduction it is demonstrated that a great number of methods for investigation of temporal integration has been used. Accordingly the results show disagreements in the size of temporal integration and in the question of frequency dependence. These differences necessitated the present normal material.

It has been customary to present the results of temporal integration measurements in a co-ordinate system where the abscissa is the logarithm of the impulse duration, and the ordinate is the threshold-shift observed. With our present knowledge of patterns in temporal integration measurements in hearing impaired ears and taking earlier investigations into account a new method of calculating temporal integration is introduced. We hope this method of calculation and presentation of temporal integration will facilitate the comparison of results from different investigators and thereby extend the use of temporal integration measurements as an audiological tool.

ZUSAMMENFASSUNG

Die Beziehung zwischen der Dauer und Intensität der Stimmulation bei der Wahrnehmung akustischer Energie wird allgemein als Temporalintegration oder Temporalsummation bezeichnet. Bei vorhergehenden Untersuchungen der Temporalintegration wurde eine große Anzahl verschiedener Methoden angewendet und infolgedessen wurden auch verschiedene Ergebnisse erzielt. Um ein Normalmaterial für künftige Vergleiche der Temporalintegration bei Schwerhörigen zu schaffen, sind 30 normalhörende Personen untersucht worden. Die Temporalintegration wurde mit Frequenzen 500, 1 kHz, 2 kHz, 4 kHz und 8 kHz mit einer Stimulationsdauer von 1 bis 1 000 msec gemessen. Die Resultate weisen darauf hin, daß bei einer Halbierung der Stimulationsdauer der Schalldruck um 3 dB bei jeder Pegelbestimmung erhöht werden muß, um die akustische Energie konstant zu erhalten. Eine deutliche Frequenzabhängigkeit der Temporalintegration wurde demonstriert.

Wir hoffen, daß die Methode zur Berechnung der Temporalintegration in diesem Versuch den Vergleich der Ergebnisse verschiedener Untersucher erleichtern und damit zur größeren Verbreitung der Temporalintegrationsmessung in der Audiometrie beitragen wird.

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CONSIDERATIONS ABOUT THE SURGICAL APPROACH IN STAPEDECTOMY

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Abstract The technical details of 1 550 stapedectomy operations for otosclerosis are discussed. The operation is based on the technique described by Shea using a Teflon piston for reconstruction. Emphasis is laid on the extreme care and precision in making a calibrated trepanation hole as well as on the trimming and the positioning of the Teflon prosthesis. The concave perilymph meniscus protects the labyrinth from the penetration of foreign particles. The fact that only the vestibular endothelium builds up the effective obturating membrane, constitutes another fundamental aspect. The shape of this membrane is greatly defined by the contact angle of the perilymph on the prosthesis.

Earlier stapedectomies were performed using a polyethylene strut or Teflon piston, after closing the oval window with a vein graft. The technique to be described in this paper has used in the last 1 550 cases.

TECHNIQUE

The operation is based on the technique described by Shea using a Teflon piston for reconstruction. Extreme care is taken to make the hole in the footplate just large enough to admit the piston and yet allow it to move freely in the centre of the oval window The Teflon prosthesis should be trimmed to the correct length. It was always attempted to preserve the tendon of the m. stapedius which was possible in about 70% of the operated cases (Marquet, 1965) It maintains the vascularity of the lenticular process of the incus and prevents the prosthesis from slipping, should the process be absent or malformed. A third advantage of the conservation of the tendon of the m. stapedius reported by Lidén et al. (1964) is a better speech discrimination in noisy conditions.

Details of the operation

1) By using an especially designed micro-hook with dimensions 0.15×0.2 mm, it is possible to achieve a correct circular trepanation of the footplate. Small bony fragments are gently removed with the hook, until the hole has been enlarged to 0 7 mm in diameter This can be done even when it proves to be necessary to thin the footplate by previous drilling (Fig 1)

By means of a set of calibrators (diameter 0 4 to 0.8 mm) designed especially for this purpose, the correct size of this hole is easily checked, without manipulating the prosthesis (Fig 2)

2) No graft is used to cover the oval window except after accidental removal of the whole foot-plate, which occurred in 5% of cases. The oval window was then covered with a vein graft

3) The length of the prosthesis is evaluated with a precision of about 0.2 mm. After one or more direct checks in the middle ear itself

Fig. 1. The calibrated hole.

the Teflon prosthesis is carefully trimmed to the appropriate length. A special fork holds the piston and facilitates its manipulation within the middle ear (Fig. 3)

4) The surgery is done under a technique of general anesthesia, called "Protected Sleep" as elaborated by Delaruelle & Marquet (1971). This technique of narcosis proves to be completely satisfactory. The subject is maintained in a state of autonomic nervous depression which at the same time guarantees an unaltered hydrodynamic state of the labyrinth. Bleeding or overflowing of perilymph are the exceptions.

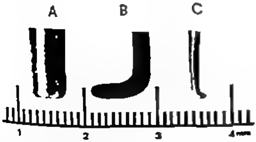

Fig. 2. (*A*) Calibrator 0.5 mm diameter. (*B*) Classical hook of 0.6 mm 0.3 mm. (*C*) Micro-hook of 0.15 mm x 0.2 mm.

Advantages

1) By the use of special instruments in this precise technique the risk of iatrogenic tearing of the vestibulum is minimal (Fig. 4).

2) As the calibrated hole is made in the centre of the footplate, rupture of the annular ligament is avoided, which means that

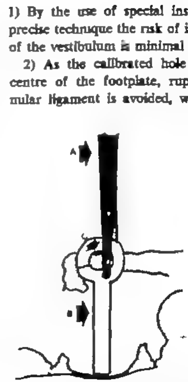

Fig. 3. The Teflon prosthesis (*B*), held by means of a specially designed fork (*A*) is trimmed to the exact length with intact footplate. Some 0... mm (checked at *C*) are added to compensate the thickness of the footplate.

there is no risk of damage due to the elevation of the vestibular endothelium, as described by House (1970) (Fig. 5)

3) The meticulous trimming of the length of the prosthesis, whose penetration into the vestibulum never exceeds 0 1 mm avoids the possibility of tearing or mechanical irritation of the vestibulum. The growth of the reparative vestibular endothelium underneath the lower extremity of the prosthesis will be guided by the meniscus of the perilymph, thus sealing off the inner from the middle ear

4) The small size of the trepanation hole protects the vestibulum after the piston is brought in position since only an extremely narrow annular opening of the vestibulum is left. Also, before the placement of the prosthesis, the small curvature of the meniscus guarantees a good protection of the labyrinth against the penetration of waste particles (see discussion below)

5) The piston is thus positioned at both of its ends. No pendulum movement can take place so that the tip remains in the centre of footplate and perpendicular to it (Fig. 6)

All these advantages ensure a good functional result in any case of correct diagnose of stapes ankylosis.

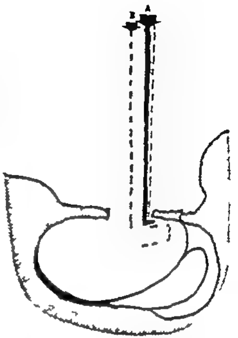

Fig 4 The risk of iatrogenic lesions when using our micro-hook (*A*) or the classical one (*B*).

Role of the Perilymph Meniscus

Protection of the labyrinth

During surgery the concavity of the meniscus offers a barrier to the penetration of foreign particles such as a piece of footplate, a waste piece or a piece of mucoperiosteum. Foreign particles with a density less than that of perilymph are pulled towards the edge of the trepanation hole, just as an air bubble is attracted towards the edge in a cup of tea. In order to obtain a concave meniscus with small curvature the trepanation hole must be small. If the hole is larger or the oval window is completely open, the curvature of the meniscus is too large to guarantee a sufficient protection, since the particles near the centre will not move towards the edge It was observed that in the case of a small trepanation hole most of the foreign particles floated to the edge. From this we can deduce that by adhesion of microscopic air bubbles on the rough surface of these extremely small particles the average

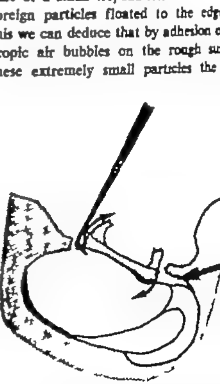

Fig 5 (Following H House). By removing the whole footplate there is a risk of elevating endothelium on the vestibular side This space (*arrow*) might be responsible for cochleo-vestibular damage.

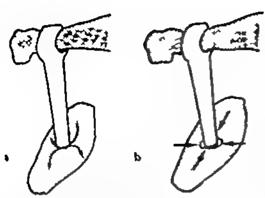

Fig. 6 (*a*) Possible pendulous effect of the prosthesis. (*b*) Well-fixed prosthesis.

density must be less than the density of perilymph.

The few particles with a density greater than that of perilymph will also stay afloat if they are small enough, just like a greasy needle on water. The surface tension in conjunction with a contact angle $\theta > 90$ produces an upward force proportional to the circumference of the particle. As the gravitational pull is proportional to the second or third power of the radius (for cylindrical or spherical particles), only extremely small pieces will float. Again the use of the micro-hook of 0.15 mm is recommended, as this instrument is the only one which produces very small waste particles.

Guide for ingrowth of vestibular endothelium

Middle ear mucosa, periosteum or implanted tissue seems to play little part in the effective closing of the defect (later paper).

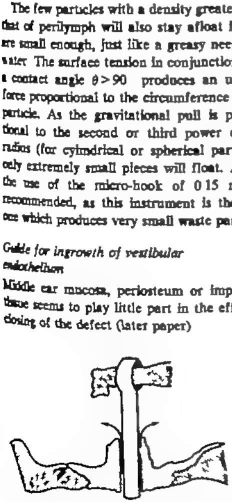

Fig. 7 Diagram showing the possibility of perilymph loss through a cuff around the prosthesis.

The defect in the endothelial lining of the labyrinth is closed by ingrowth from its edges, underneath the tip of the piston and following the free surface of the perilymph. The contact angle of perilymph on the prosthesis is very important as it will greatly define the shape of the meniscus (Van Camp et al., 1972). This factor played an important role in the choice of Teflon. A *clean* Teflon surface, obtained automatically by cutting the piston to the appropriate length, catalyses biologically the growth of the reparative endothelium. All these factors can account for the fact that not a single case of fistula was proved. We must keep in mind that the mean stapedial amplitude under normal loading is about 10 A at a sound level of 80 dB (Rubinstein et al., 1966). The picture which is generally given of a larger amplitude, like that obtained when checking the complete reconstruction with an instrument, can only lead to faulty deductions concerning the function of the reparative membrane.

A free meniscus is not formed when the oval window has been closed with a graft, after removing the whole footplate. The middle ear mucosa encroaches over the graft and often forms a cuff around the prosthesis (Fig. 7).

If the prosthesis is too long or if for any reason an occasional perforation of the graft is not completely closed by the reparative endothelium, a perilymph loss through such a cuff is possible.

CONCLUSION

We are convinced that many sensorineural complications occurring after stapes surgery can be attributed to disregarded iatrogenic lesions. We are able to say that all the above mentioned theoretical considerations are in good accord with the clinical findings. A series of 1550 cases has been carried out strictly following the described technique. Immediate postoperative vertigo and overhearing are exceptional and disappear within a week. Only in 1 patient did it last for a long period. The hearing improvement on audiogram is

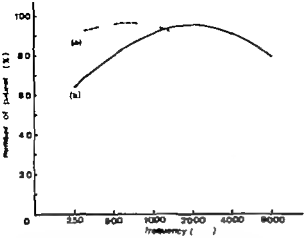

Fig 8 Number of patients (%) with closure of the air–bone gap to 10 dB or less for different frequencies. (*a*) In the series of vein graft interposition with complete stapedectomies. (*b*) In the series performed with the described technique, without any graft on a calibrated hole.

good often there is a residual air–bone gap in the lower frequencies, but complete closure in the higher frequencies. The patient therefore enjoys greater improvement of speech discrimination in comparison with techniques utilizing vein graft interposition (Fig. 8)

On the other hand this technique is much more secure regarding the classical stapedectomy complications. We regret having one case of a noted sensorineural hearing loss in this case of otosclerosis the patient had already presented some preoperative vestibular disorders. To our knowledge we do not have any proved case of fistula.

These results compare favourably with the series where the oval window was covered with a vein graft. In this series, sensorineural hearing loss occurred in 2% of patients and fistula in 4% of patients.

RESUME

Cette étude se rapporte à une série de 1 550 cas d'otoscléroses opérée selon une technique basée sur la technique classique de Shea, mais caractérisée par le soin et la précision toute particulière, requise pour le calibrage de la trepanation et pour la mise en place de la prothèse. Des avantages de cette technique sont successivement envisagés. Le rôle protecteur que joue pour le labyrinthe la concavité du ménisque, comme barrière contre la pénétration de particules étrangères est étudié. Finalement un autre aspect essentiel est également envisagé, à *savoir que la seule membrane* oblitérant réellement la fenêtre ovale provient de l'endothelium vestibulaire et que donc, ici également, des paramètres physiques, entre autre l'angle de contact (θ), jouent un rôle important.

ZUSAMMENFASSUNG

Dieser Artikel behandelt eine Studie über 1550 Fälle von Otosklerose, bei denen die Operationsmethode mit dem allgemein üblichen „Shea-Piston" angewandt wurde. Hierbei wurde besonders auf Präzision geachtet, sowohl bei der Trepanierung als beim Ansetzen und Auf-Abstand Bringen der Prothese. Die Vorteile dieser Operationstechnik werden besprochen. Die Abschirmung des Labyrinths gegen Abfallteilchen durch den konkaven Perilymphen-Meniskus wird dargelegt. Ausserdem wird besonders darauf hingewiesen, dass es nur das vestibulare Endothelium ist, welches *die abdichtende Membrane bildet. Die* Bildung dieser Membrane wird auch von dem Kontaktwinkel der Perilymphe zur Prothese bestimmt.

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QUALITATIVE UNTERSUCHUNGEN DER VERBINDUNGSWEGE DES SUBARACHNOIDALRAUMES MIT DEM LYMPHATISCHEN SYSTEM DES KOPFES UND DES HALSES

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Abstrakt. Die Injektion einer licht- und elektronenmikroskopischen Tracersubstanz in den Liquor cerebrospinalis von Mäusen, Ratten, Meerschweinchen und Kaninchen gestattet es, neben den bekannten Abflußwegen des Liquors über die Arachnoidalzotten und meningealen Venen anatomische Verbindungen zum Lymphsystem des Kopfes und Halses zu demonstrieren. Als Lymphabflußwege des Liquors dienen die Perineuralräume der großen Hirnnerven insbesondere die Perineuralscheiden der Fila olfactoria, die sich in die Lymphgefäße der Nasenschleimhaut ableiten, die Perineuralräume der Nervi acustici, die mit den perilymphatischen Räumen des Innenohres und den Extrazellularräumen und Lymphgefäßen der Mittelohrschleimhaut in Verbindung stehen, sowie zahlreiche subepitheliale Lymphspalten der Nasen-Rachenschleimhäute. Auch die Perineuralscheide des Nervus opticus und die mit ihm in Verbindung stehenden Lymphgefäße der Tenonschen Kapsel waren als Fortsetzung des Subarachnoidalraumes zu erkennen. Es zeigte sich eindeutig eine Abhängigkeit der Abflußgeschwindigkeit von der in den Liquor applizierten Teilchengröße. Vergleichsweise untersuchte Lymphknoten aus anderen Körperregionen enthielten keine Kontrastpartikel. Im Gegenversuch gelang es bei gleicher Applikationsmenge des Kontrastmittels in die Blutbahn nicht, den Tracer nach entsprechend kurzer Zeit in den Lymphknoten zu finden. Lediglich die Milz und die Leber enthielten die intravasal applizierten Tracersubstanzen. Zur Demonstration, daß auch zelluläre Elemente die Liquor-Lymphpassage überwinden können, applizierten wir Yoshida-Tumorzellen in den Liquor und konnten damit nach wenigen Tagen eine Meningitis carcinomatosa erzeugen und feststellen, daß sich die Zellen entlang der gleichen beschriebenen Wege ausbreiten. Die Bedeutung dieser Liquor-Lymphverbindungen für die Pathogenese verschiedenster neurotroper bakterieller und viraler Infektionskrankheiten wird diskutiert.

Herrn Prof. Dr. med. J. Berendes zum 65. Geburtstag gewidmet.

Der Liquor cerebrospinalis gilt als das Sekretionsprodukt der Plexus chorioidei und der pialen Gefäße (Schaltenbrand, 1949). Sein Gehalt an Elektrolyten und Proteinen variiert sehr stark und ist abhängig von der jeweils dominierenden regionalen Sekretion oder Resorption des Ependyms, der Arachnoidalzotten oder venöser meningealer Gefäße. Als Barriere bei der Liquorrückresorption fixierte man die sogenannte Liquor-Blutschranke, die wie beispielsweise Shabo et al. (1969) zeigten, im cerebralen Bereich zum Teil in den Arachnoidalzotten zu finden ist. Hierbei handelt es sich um eine selektive Filtrationsbarriere zwischen dem Liquor cerebrospinalis und dem venösen Systemkreislauf, die dafür Sorge tragen soll, daß keine hirnspezifischen Abbauprodukte ohne vorherige zelluläre Umwandlung oder Denaturierung in das Blut übertreten können. Doch hatten bereits Schwalbe (1869, 1870, 1872), Key & Retzius (1875) in Untersuchungen am toten Tier auf einen Zusammenhang des Liquorraumes mit den Lymphgefäßen der Nasenschleimhaut hingewiesen. Jossifow (1930) deutete an, daß es Lymphgefäße im Kopf-Halsgebiet und im retroperitonealen Raume gäbe, welche mit den Perineuralscheiden der großen Hirnnerven und der Spinalnerven in Verbindung stünden. Ähnliche Befunde erhoben Hoffmann & Thiel (1956) in ihrer Untersuchung über die Flüssigkeitsverbindungen der Peri-

neuralräume der Fila olfactoria mit den Lymphgefäßen der Riechschleimhaut. In umgekehrter Weise gelang Földi (1963) und Földi et al. (1967 1968 1969) der Nachweis, daß nach Unterbindung sämtlicher Lymphbahnen des Halsgebietes bei Maus, Katze und Hund die Symptomatologie der sog. lymphogenen Enzephalopathie auftritt einem Krankheitsbild, dessen *Symptomatologie Quincke (1893) beim* Menschen als seriöse Meningitis und Nonne (1904) als Pseudotumor cerebri bezeichnet hatten. Hierbei kommt es zu ophthalmologischen Veränderungen (Ödem der Bindehaut, der Papille und der Retina, Permeabilitätsstörung der Blut Augenkammer Schranke, Exophthalmus) zu einer herabgesetzten Krampfschwelle, zu Veränderungen im EEG zu einer Herabsetzung der bedingten Reflextätigkeit und pathologisch-anatomischen Veränderungen im Bereich der perivasculären Neuroglia.

Unsere kürzlich mitgeteilten röntgenologischen Demonstrationen der Liquor Lymphverbindungen (Arnold et al. 1971) ließen *übersichtlich die verschiedenen Zusammen*hänge mit dem Lymphsystem des Kopf Halsgebietes erkennen, Zusammenhänge, die wir in dieser Mitteilung histologisch demonstrieren wollen.

MATERIAL UND METHODE[1]

[illegible]ie Untersuchungen wurden an Mäusen Rat[illegible] Meerschweinchen und Kaninchen durch[illegible] Die Tiere wurden in Nembutal- oder Äthernarkose operiert. Die Freilegung der Membrana atlanto-occipitalis zur Suboccipitalpunktion erfolgte durch einfachen Querschnitt über der Hinterhauptsschuppe und Wegpräparieren der Nackenmuskulatur Für die lichtmikroskopische Untersuchung injizierten wir 50–100 μl im Verhältnis 1 3 verdünnter käuflicher Tusche (Romeis, 1968) oder Try*panblau. Für die elektronenmikroskopische* Untersuchung verwandten wir als Kontrastmittel Thorotrast. In der hier berichteten Studie werteten wir nur Kurzzeitversuche aus, welche sich auf 1 bis 15 Minuten beliefen. Daneben injizierten wir bei 8 Ratten Yoshida-Sarkomzellen (1 mm³ entsprechen 10⁵ Zellen), die wir dem Peritonealraum von Tumortestieren frisch entnommen hatten.

Nach der zisternalen Injektion wurden die *Tiere für die lichtmikroskopische Aufarbei*tung dekapitiert, die uns interessierenden Gewebestückchen entnommen und in Bouin scher Lösung fixiert. Soweit nötig erfolgte die Entkalkung in Salpetersäure die Entwässerung und Einbettung in üblicher Weise über Alkohol, Methylbenzoat, Benzol in Paraffin Für die elektronenmikroskopische Untersuchung bewährte sich die korporale Perfusionsfixation mit 2,5 %igem Glutaraldehyd (Karlsson & Schultz, 1965) oder mit 6,4 %igem Glutaraldehyd (Rewcastle, 1965). Die Nachfixierung erfolgte in 1 %igem Osmiumtetroxyd (Palade 1952) die Einbettung in Epon 812 (Luft, 1961). Die mit Bleicitrat (Reynolds, 1963) *und Uranylacetat* (Huxley & Zubay 1961) nachkontrastierten Ultradünnschnitte wurden mit einem Zeiss EM 9 A elektronenmikroskopisch untersucht.

BEFUNDE

Bereits wenige Sekunden nach *Injektion von* Trypanblau, kolloidaler Tusche oder Thorotrast in die Cisterna cerebellomedullaris gelangt diese über den Aquaeductus perilymphaticus und entlang dem Subarachnoidalraum des Nervus acusticus in die perilymphatischen Flüssigkeitsräume des Innenohres. Dort erfahren sie ihre Ausbreitung von basal nach apikal — soweit der Tracer über den Aquaeductus perilymphaticus in die Scala tympani gelangt ist — oder aber die Partikelchen gelangen aus dem Modiolus über das Ganglion in den Rosenthal'schen Kanal zentrifugal in die perilymphatischen Räume der Scala tympani (Einzelheiten über die Ausbreitung im Innenohr vgl. v Ilberg & Vosteen, 1969 Ar-

[1] Frl. G Frank und Fr S. Meyer danken wir für wertvolle technische Assistenz.

Abb. 1 Elektronenmikroskopisch vergrößerter Ausschnitt aus dem Spatium perilymphaticum ligamenti spiralis der Scala tympani. Die Flüssigkeitsräume des Ligamentum spirale enthalten 3 Minuten nach Injektion in den Liquor cerebrospinalis das Thorotrast und man kann rechts im Bild die mikropinozytotische Aufnahme von Flüssigkeit mit Thorotrastpartikelchen in das Lumen einer Kapillare beobachten. *P* Perilymphe; *T* Thorotrast → Pinozytosebläschen im Kapillarendothel. *Lr.* Fasernetz des Ligamentum spirale (Meerschweinchen).

nold & v. Ilberg, 1971 *b*). Lichtmikroskopisch läßt sich eine Abwanderung der Tuschepartikelchen entlang der Perivasculärräume der modiolären Spiralvenen verfolgen. Elektronenoptisch erkennt man zusätzlich eine Aufnahme der Thorotrastpartikelchen in venöse Kapillaren des Ligamentum spirale oder im Bereich der endothelähnlichen Auskleidung der Perilymphräume (Abb. 1). Schließlich läßt sich der Tracer aus den perilymphatischen Flüssigkeitsräumen der Scala tympani im Bereich des Fenestra rotunda in die extrazellulären Flüssigkeitsräume und Lymphgefäße der Mittelohrschleimhaut hinein verfolgen (Abb. 2).

Handelt es sich um lichtmikroskopisch sicht

Abb. 2 a–d. (*a*) Elektronenmikroskopischer Ausschnitt aus dem Ganglion spirale vom Meerschweinchen (2. Windung). *L*, weite Extrazellularräume, die von den Fortsätzen der Schwannschen Zellen begrenzt werden. *Gz*, myelinisierte Ganglienzellen.
(*b*) 3 Minuten nach Injektion von Thorotrast T in den Liquor enthalten die Extrazellularräume im Bereich des Ganglion spirale den Tracer. *M*, Mitochondrium (Meerschweinchen).
(*c*) Ausschnitt aus der epithelialen und subepithelialen Region der Mittelohrschleimhaut am Paukenboden (Meerschweinchen). 1–3 Minuten nach Injektion von Thoriumdioxyd in den Liquor ist der gesamte Extrazellularraum und der Inhalt von Pinozytosebläschen im Cytoplasma der Epithelzellen mit Thorotrastpartikelchen gefüllt. *Pv* pinozytotische Vesikel. *K* kollagene Fasern. *Bm* Basalmembran. Lumen der Bulla tympanica.
(*d*) 10 Minuten nach Tuscheinjektion in die Cisterna cerebellomedullaris sind die Lymphknotensinus mit den Kohlepartikelchen ausgefüllt. (Meerschweinchen).

bare Farbpartikel, so breiten sich diese in den Lymphgefäßen des subepithelialen Raumes der Mittelohrschleimhaut aus und lassen sich bis zu den regionalen Lymphknoten darstellen (der Weg verläuft entlang der Lymphgefäße der Tuba Eustachii zur Pharynxschleimhaut oder über das Trommelfell — äußerer Gehörgang zu den retroaurikulären Lymphknoten (Most, 1905). Zusätzlich erkennt man ultrastrukturell, wie das Thorotrast auch zellulär vom Epithel der Mittelohrschleimhaut aufgenommen und an die Oberfläche ausgestoßen wird.

3–5 Minuten nach der Injektion einer Farbstofflösung in den Liquor cerebrospinalis färben sich makroskopisch erkennbar die retroaurikulären Lymphknoten mit dem injizierten Farbstoff an. Es ist anzunehmen, daß diese ihren Lymphzufluß nicht nur von den lateralen Anteilen der Paukenhöhle und der

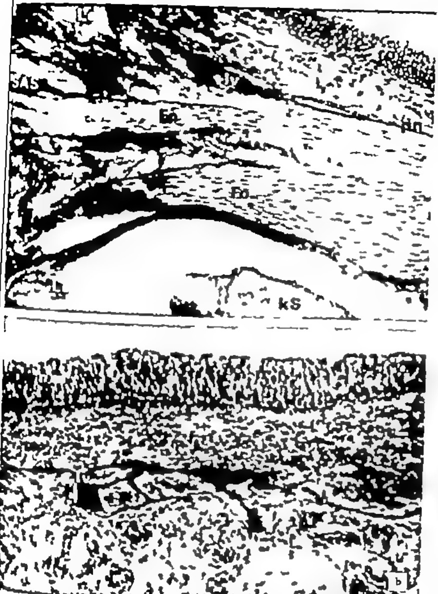

Abb. 3 a–b (*a*) Darstellung der Perineuralräume der Fila olfactoria und der mit ihnen kommunizierenden Lymphgefäße der Regio olfactoria 5 Minuten nach Tuscheinjektion in den Liquor cerebrospinalis der Cisterna cerebello-medullaris. *Lc* Knochen der Lamina cribrosa, *SAS* Übergang des Subarachnoidalraumes des Riechhirns in den Perineuralraum der Fila olfactoria (Fo) *lv* Lymphgefäße, die mit dem Perineuralraum in Verbindung stehen, *ro* Riechepithel *pn* Perineuralraum, *kS* knöcherner Anteil des Septum nasi

(*b*) Entsprechender Ausschnitt aus der Nasenschleimhaut der lateralen Nasenwand. Auch hier sind die Lymphspalten thrombenartig mit Tuschepartikelchen ausgefüllt. *nm*, Epithel der Nasenschleimhaut, *lv* Lymphgefäße.

Trommelfelles erhalten, sondern daß auch eine Verbindung zum Perineuralraum des Nervus facialis besteht. Eröffnet man nämlich von retroaurikulär die Paukenhöhle und durchtrennt dann den Nervus facialis bei seinem Austritt aus dem Labyrinthblock, so erkennt man unmittelbar nach Injektion einer Farbstofflösung in den Liquor wie aus dem Kanal des Nervus facialis angefärbter Liquor heraustropft. Bei all diesen Ver-

Abb. 4 a, b. Aus dem Perineuralraum der Riechnerven tritt die Tusche in Lymphgefäße unterhalb des Riechepithels über und kann bis zwischen die Sinnes- und Stützzellen des Riechepithels (Abb. b) verfolgt werden.

auf, daß die Lage des Tieres eine nicht unerhebliche Rolle bei der Füllung der abführenden Lymphgefäße spielt. Injiziert man beispielsweise einem Meerschweinchen in Seitenlage Trypanblau in die Cisterna cerebello-medullaris, so färbt sich zuerst die Cochlea und weite Teile der Schleimhautauskleidung der Bulla auf der nach unten gelegenen Seite blau an, wogegen die Lymphgefäße der Gegenseite sich erst später anfüllen. Liegt das Tier dagegen in ventro-dorsaler Lage, so färbt sich die Schleimhaut beiderseits gleichmäßig.

Legt man vor der Injektion einer Farbstofflösung in die Zisterne durch Abtragen des Nasendaches die Nasenschleimhäute frei und injiziert dann die Farbstofflösung, so kann man unmittelbar darauf unter dem Operationsmikroskop die Füllung des Lymphgefäßnetzes im gesamten Nasenschleimhautbereich verfolgen. Histologische Schnitte durch die Lamina cribrosa und angrenzende Riechschleimhaut lassen erkennen, wie die Tusche aus den Perineuralräumen der Fila olfactoria in die Lymphgefäße der Riechschleimhaut übertritt und in das Lymphsystem der Nasenschleimhaut abgeleitet wird (Abb. 3, 4, 5 a, b). Auch im Verlaufe des Nervus opticus erkennt man dessen Perineuralscheide bis zum Eintritt des Nerven in die Tenonsche Kapsel angefüllt mit Farbstoffpartikelchen. Lichtmikroskopisch konnte kein Eindringen des Farbstoffes in den Augapfel gesehen werden. Elektronenmikroskopische Untersuchungen darüber stehen noch aus. Schließlich läßt sich nach vorheriger Freilegung des Halses zur Darstellung der tiefen Halslymphknoten beim lebenden Tier 3–5 Minuten nach Injektion der Farbstofflösung in den Liquor bereits makroskopisch die Injektion zarter Lymphgefäße erkennen, die neben der Vena jugularis auf dem Nervus vagus verlaufen. Der Farbstoff dringt sehr rasch in die tiefen Halslymphknoten ein und füllt die Kapselräume (Abb. 6). Läßt sich auch im Lichtmikroskop nach so kurzer Zeit nur eine Füllung der Randsinus darstellen, so findet man im Elektronenmikroskop bereits 5 Minuten nach Injektion

Abb 5 a, b (*a*) Weite Lymphspalten im subepithelialen Bindegewebe der Nasenschleimhaut im Bereich des vorderen Septumanteiles sind thrombenartig mit Tusche ausgefullt (Kaninchen). *L*, Lumen der Nasenhohle.

(*b*) In engem Kontakt zum lymphatischen Gewebe (*Ly*) unterhalb des Epithels der Epipharynxschleimhaut erkennt man die liquorableitenden weiten Lymphspalten (Kaninchen) *F* Fettgewebe *Bg* Bindegewebe *K*, Kapillare.

Thoriumdioxyd in den Liquor das Kontrastmittel auch innerhalb der Markräume des Lymphknotens interzellulär wieder Aus den Randsinus selbst werden die 40 A großen Partikelchen sehr schnell von den Retikulumzellen phagozytiert und in großen Lyspaketen angereichert (Abb 7 *a*, *b*) sei bemerkt, daß sich insbeso

Abb. 6 Makroskopische Abbildung des Halsitus eines lebenden Meerschweinchens 15 Minuten nach Tuscheinjektion in die Chisterna cerebello-medullaris. *T* Trachea

Maus auch die retroperitonealen Lymphknoten nach Farbstoffinjektion in den Liquor anfärben. Diese Lymphknoten erhalten ihren Zufluß aus den Perineuralscheiden der Spinalnerven Appliziert man dagegen Aszitestumorzellen bei Mäusen intrathekal so sieht man 3 Tage später daß die Tumorzellen ebenfalls entlang der Perineuralräume der großen Hirnnerven entlang des Ductus perilymphaticus zu den Perilymphräumen und auf direktem Wege entlang von Lymphgefäßen die im Bereich des Foramen jugulare aus dem Subarachnoidalraum mit dem Nervus vagus und der Vena jugularis austreten zu den regionären Halslymphknoten gelangen und sich dort metastatisch absiedeln. Von neuropathologischer Seite gesehen ist bemerkenswert, daß die Tumorzellen entlang der meningealen Gefäße in die Hirnrinde eindringen und bis in die weiße Substanz perivasculär invasiv vorwachsen (Abb. 8).

Im Gegenversuch injizierten wir 1 ccm Tusche intravenös, fanden aber bis zu 30 Minuten später keine Tuschepartikelchen in den Halslymphknoten. Lediglich die Milz und die Leber hatten den Farbstoff eingelagert.

DISKUSSION

Unsere Untersuchungen haben gezeigt, daß das sog äußere Liquorsystem, der Subarachnoidalraum einen sehr rasch funktionierenden mit unseren Methoden qualitativ erfaßten Abflußweg in das Lymphsystem des Kopf Halsgebietes hat. Auch Hoffmann & Thiel (1956) konnten an der lebenden Katze den direkten Liquorabfluß in das Lymphsystem der Riechschleimhaut demonstrieren Andererseits sind uns die sehr zahlreichen Untersuchungen von Földi (1963 1969) bekannt, der nach Unterbindung sämtlicher erreichbarer Lymphknoten und Lymphabfluß-

Abb. 7a, b (a) Elektronenmikroskopischer Ausschnitt aus dem Randsinus eines Lymphknotens (Meerschweinchen). In den Flüssigkeitsräumen der Lymphknotensinusoide erkennt man neben Eiweißniederschlägen zahllose Thorotrastpartikelchen 3 Minuten nach Injektion in den Liquor. *R* Retikulumzelle; *Lz* Lymphozyt; *Ly* Lymphflüssigkeit mit Thorotrast

(b) Unkontrastierter elektronenmikroskopischer Dünnschnitt aus dem Reaktionszentrum eines Lymphknotenmarklagers. Im Gegensatz zu den 400 Å messenden Tuschepartikelchen dringen die ca. 40 Å großen Thorotrastpartikel bis in die Interzellularräume des Marklagers vor (Meerschweinchen).

Abb 8 *a*, *b* 3 Tage nach Injektion von Yoshida Sarkomzellen in die Cisterna cerebello-medullaris (Ratte) hat sich eine Meningitis sarcomatosa mit invasivem Vorwachsen der Sarkomzellen entlang der pialen Gefäße ausgebildet ( ). Die entsprechenden Halslymphknoten zeigen sarkomatöse Absiedelung der Tumorzellen (*b*).

wege des Kopfes neuropathologische Veränderungen im Sinne eines Ödems des ZNS aufzeigte. Hier soll es zu einem Papillenödem kommen wogegen die alleinige Unterbindung der Vena jugularis dieses Symptom nicht erzeugt. Weitere Hinweise auf einen Zusammenhang zwischen dem Lymphsystem der Nasenschleimhaut und dem Liquor beschrieben Yoffay (1958) Orosz et al. (1957) Seki (1963) und Brierley & Field (1948) Daß die aufgezeigten Verbindungswege auch beim Menschen eine Rolle spielen könnten darauf verweisen u. a. Putnam (zit. Schaltenbrand, 1949) Dontenwill (1952) berichtet von einem Kinde, bei dem es infolge eines Ikterus gravis neonatorum zu einer intracerebralen Blutung mit Einbruch in den III Ventrikel und Hydrocephalus gekommen war Er fand in diesem Falle Haemosiderinablagerungen in den Peri- und Endoneuralräumen der Nerven des Plexus

lumbosacralis und Plexus brachialis. Auch der Perineuralraum des Nervus vagus enthielt diffuses Haemosiderin. In den cranialen Halslymphknoten sowie in den den Halsvenen unmittelbar benachbarten Lymphknoten fanden sich Haemosiderinablagerungen. Der Verfasser weist darauf hin, daß diese Wege auch von zellulären Elementen beschritten werden können, da er in den Lymphgefäßen Fettkörnchenzellen als Zeichen einer Phanerose fand. Die physiologischen Liquorabflußwege wurden in diesem Falle also nicht nur durch die gespeicherten und freien Haemosiderinablagerungen sondern auch durch abgebautes Hirngewebe (Makroglia) weitgehend verstopft und zeichneten für die Entwicklung des Hydrocephalus als Folge der Liquorabflußbehinderung bei dem beschriebenen Fall mitverantwortlich. Schließlich soll auch auf die Untersuchungen von Speransky (1950) verwiesen werden, der Farbstoffinjektionen in den Liquor an menschlichen Leichen vornahm und ähnliche Abflußwege fand, wie die oben genannten. Daß auch der umgekehrte Weg nämlich der Übertritt von Partikelchen aus dem Lymphsystem der Nasenschleimhaut in den Liquor cerebrospinalis möglich ist, konnte durch Injektionen einer radioaktiven Substanz in die Nasenschleimhaut bewiesen werden. Bereits kurze Zeit später war das radioaktive Material im Liquor cerebrospinalis meßbar und zwar in weitaus höherer Konzentration als nach intravasaler Applikation des Isotops (Orosz et al. 1957 Czernjawska, 1970). Unsere Untersuchungen lassen den Schluß zu daß ein Großteil des Liquor cerebrospinalis auch über das lymphatische System des Kopf Halsgebietes abgeleitet werden kann. Dabei haben insbesondere die Sinnesorgane Innenohr Regio olfactoria und Augenkammer (Schaltenbrand, 1949) eine enge Beziehung zum Liquorraum aufzuweisen. Als erste Barriere einer möglicherweise in Frage kommenden Liquor Blutschranke fungieren bei dieser Ableitung die tiefen Halslymphknoten, welche als Sammelbecken der Lymphe des Nasenrachenraumes anzusehen sind. Wie ultrastrukturell erkennbar sind die Reticulumzellen der Randsinus bestrebt, die Lymphe von partikulären Elementen zu befreien.

Unsere Befunde geben auch zu der Überlegung Anlaß was funktionell geschehen könnte, wenn es beispielsweise infolge einer Lymphadenitis colli zu einem verzögerten Abfluß der Lymphe und damit zu einem Lymphrückstau kommt. Es wäre denkbar daß dann Mikroorganismen, welche beispielsweise das Epithel der Nasenschleimhaut bereits durchwandert haben und in die Lymphgefäße eingedrungen sind, besonders leicht retrograd in den Subarachnoidalraum vordringen. Wie oben erwähnt ist dieser Weg mittels Isotopen experimentell bewiesen. In ähnlicher Weise hat u. a. Rosemann (1964) darauf hingewiesen, daß maligne Geschwülste des Nasenrachenraumes entlang der Nervenscheiden und perivaskulären Lymphscheiden in den Subarachnoidalraum vordringen können also den gleichen Weg in umgekehrter Richtung benützen, wie er im Experiment dargestellt wurde

Die Frage, welcher Weg des Liquorabflusses quantitativ überwiegt, nämlich der über die Arachnoidalzotten und meningealen Venen oder der über die zahlreichen Verbindungen zum Lymphsystem des Kopf Halsgebietes, bleibt im Augenblick noch offen und ist Gegenstand gegenwärtiger Untersuchungen.

Abschließend soll kritisch dem möglichen Einwand entgegengetreten werden, es könnte sich beim Übertritt des farbstoffmarkierten Liquors in das Lymphsystem des Kopf-Halsgebietes um die Folge des angewandten Injektionsdruckes handeln. Um diesen immer wieder gestellten Einwand zu entkräftigen, haben wir uns die physiologisch bekannte Tatsache zunutze gemacht, daß ein venöser Rückstau im Kopf Halsgebiet (vergl. Queckenstedt'scher Versuch), beispielsweise aktiv hervorgerufen durch Bauchpressen, Atemanhalten, Husten oder passiv durch Druck auf das Abdomen und den Thorax des narkotisierten Tieres erhebliche Liquordrucksteigerung nach sich zieht (Beentjes, 1972). Nach Freilegen

der Membrana atlanto-occipitalis beim Meerschweinchen wurde in die Membran eine kleine Perforation gesetzt. In diese wurde ein sich nach oben trichterförmig erweiterndes Polyvenylschläuchlein etwa 0,5 mm weit in die Zisterne eingeführt und die Ränder der Perforation mit einem Gewebeklebstoff (Histacryl) abgedichtet. Unter vorsichtigem kontinuierlich anhaltendem manuellem Druck auf das Abdomen des Tieres steigt der Liquordruck und damit in dem Polyvenylschlauch der Liquor nach oben. Dieser wird mittels einer Mikropipette abgesaugt und dafür eine entsprechende Menge Farbstofflösung in den Trichter eingefüllt (meist 100 bis 500 μl). Unter Nachlassen des Druckes auf das Abdomen des Tieres sinkt der Flüssigkeitsspiegel in dem Polyvenyltrichter langsam wieder auf das ursprüngliche Niveau und saugt damit die Farbstofflösung in die Zisterne ein. Nach 3–5 Minuten zeigt sich auch mit dieser Methode eine mikroskopisch sichtbare Tinktion der abführenden Lymphwege und der tiefen Halslymphknoten, bereits nach 30 Sekunden haben sich ohne Anwendung von Druck die perilymphatischen Räume der Cochlea bis zur Spitze hinauf angefärbt. Unter dem Operationsmikroskop erkennt man die zarte Füllung des Lymphgefäßnetzes im Bereich der Mittelohrschleimhaut.

Nachdem wir festgestellt hatten, daß also für den Übertritt unserer Farbstoffpartikelchen in das Lymphsystem des Kopf-Halsgebietes kein Druck nötig war, konnten wir ohne Bedenken die von uns angewandte geringe Injektionsmenge von 50–100 μl mittels einer Tuberkulinspritze in die Zisterne injizieren. Verschiedentlich haben wir auch zur Druckentlastung beide Fenestrae rotundae eröffnet. Zum anderen wurde der geringe Überdruck in der Cisterna cerebello-medullaris durch das Zurückziehen der Nadel nach der Injektion und der danach resultierenden Perforation in der Membrana atlanto-occipitalis entlastet. Schließlich soll festgehalten werden, daß die Tiere den unter sterilen Kautelen durchgeführten Eingriff ohne offensichtliche Folgen beliebig lange überleben und sich dabei in ihrem Verhalten (Freßlust, akustische und optische Reaktionen) in nichts von ihren normalen Artgenossen unterscheiden. Würde es tatsächlich zu einer erheblichen intrakraniellen Drucksteigerung kommen, so wäre es in einem geschlossenen System, in dem sich der Druck nach den physikalischen Gesetzen in allen Richtungen gleichmäßig ausbreitet, nicht möglich, daß, wie oben erwähnt, die nach unten liegende Bulla tympanica sich jeweils bei Kopfseitenlage stärker und frühzeitiger anfärbt als die gegenüber liegende.

SCHLUßFOLGERUNGEN

1. Der Liquor cerebrospinalis steht in direktem Zusammenhang mit dem Lymphsystem des Kopf-Halsgebietes.
2. Besonders enge Beziehungen bestehen zu den Sinnesorganen Innenohr, Regio olfactoria und Auge.
3. Als Liquor-Blutschranke kommen also neben den Arachnoidalzotten auch die tiefen Halslymphknoten infrage.
4. Über die aufgezeigten Verbindungen des Liquors zum retikuloendothelialen System der Lymphknoten könnten sich neue immunbiologische Aspekte für das Zentralnervensystem ergeben.

RÉSUMÉ

Par l'injection d'un tracé imperméable pour lumière et rayons électroniques également dans le LCR des souris, des rats, des cobayes et des lapins, on peut démontrer facilement qu'il existe plusieurs connections largement ouvertes entre le LCR de l'espace sous-arachnoïdien et le système lymphatique de la région de la tête et du cou (au dehors du passage bien connu par les villosités arachnoïdiennes et les veines méningées). Après un moment très court (secondes à minutes) le tracé injecté dans le confluent postérieur était trouvé dans les ganglions lymphatiques du cou par la méthode microscopique optique et électronique. Il était possible de poursuivre les particules du ... le long d... espaces périneuraux du nerf olf... nerf op... du nerf auditif et du nerf fac... ...s lymphatiques. De là elles sor... ...aces périlymphatiques

à l'oreille interne, dans les vaisseaux lymphatiques la muqueuse de l'oreille moyenne (comme nous avons décrit récemment), dans la muqueuse nasale et dans les vaisseaux lymphatiques de la muqueuse du ... La vitesse de l'écoulement du tracé ... t de son diamètre. Des éléments cellulaires ont pris les mêmes voies par les passages mentionnés ... Des cellules du sarcome Yoshida on été injectées dans le LCR à la même manière. Elles ont provoqué une méningite sarcomateuse et une altération sarcomateuse des ganglions lymphatiques du cou dans quelques jours.

La signification des connections étroites entre le LCR et la lymphe à travers la pathogénèse des infections différentes neurotropes bactérielles ou virales devrait être considérée sérieusement.

SUMMARY

By the injection of a light- and electron dense tracer into the CSF of mice, rats, guinea pigs and rabbits, it could be shown that there exist many widely opened connections between the CSF of the subarachnoid space and the lymphatic system in the region of the head and neck. By means of this simple method, the tracer could be demonstrated light and electronmicroscopically in the lymphnodes of the neck within very short time (seconds to minutes). It was possible to follow the particles of the tracer on their way to the lymphnodes along the perineural spaces of the fila olfactoria, the optic nerve, the acustic nerve and the facial nerve. From the CSF they also enter into the perilymphatic spaces of the inner ear and reach the lymphatic vessels of the middle ear mucosa; the flowing rate of the tracer was dependent on its diameter. Cellular elements were also able to find their way through the described passages.

Yoshida sarcoma cells were injected into the CSF in the similar manner. Within 3 days these cells caused meningitis sarcomatosa and sarcomatous alteration of the lymphnodes of the neck. Many lymphatic vessels of the nasopharynx and the perineural spaces of the acustic, optic and olfactoric nerves were filled with these cellular elements. The significance of the relationship between the CSF and the lymphatic system of the head and neck as to infections caused by bacteria or virus should be considered.

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LONG-TERM POSTOPERATI\ I L I' FOLLOWING SELECTIVE SECTION OF THE VESTIBUL \ I\ MENIERE'S DISEASE

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Abstract. A material, consisting of 15 patients, had preoperatively suffered from severe bout vertigo, and from tinnitus and loss of hearing w s investigated from 3 to 7 years after selective vestibula nerve section in Ménière s disease. Vertigo bout disappeared in all patients; tinnitus improved in 73 and remained unchanged in 27%. In 80% there was no change as regards hearing, and in 20% it deteriorated. This demonstrated that a selective nerve section gives better long-term results than other opera tive methods. Moreover it indicates that although the operation may not bring about a cure, in most cases it will prevent the disease from progressing.

Ménière's disease is now generally considered to depend on an endolymphatic hydrops, but the cause of this is still not clear and is probably due to several factors. Most patients are given conservative medical treatment, but in a smaller number of cases an operative treatment is the only resort because despite the medical treatment the patients are unable to continuing working.

During recent years principally 6 different operative techniques have been developed.

1 Destruction of the whole labyrinth (labyrinthectomy and Cawthorne's operation I and II).
2. Section of the vestibular nerve
3. Ultrasound treatment.
4. Shunt operation through opening of the endolymphatic sac with or without insertion of a plastic tube.
5 Sacculotomy
6. Cryosurgery

Destruction of the whole labyrinth by labyrinthectomy or the so-called Cawthorne s operation results in complete relief from vertigo in all patients, but causes total deafness in the operated ear

Section of the statoacoustic nerve has given good results in respect of vertigo Olivecrona (1943) reported on 125 patients in 96% of whom the vertigo had completely disappeared, whereas 15% were deaf and in 16.5% hearing was reduced postoperatively The tinnitus was unchanged in most of the cases.

Green & Douglas (1951) made a retrospective investigation of patients with Ménière s disease who were operated by Dandy with selective nerve section. They found that 90% of them were completely free from vertigo 5–20 years postoperatively

Fisch (1970) reported the results obtained in 37 patients with Ménière s disease who underwent so-called vestibular neurectomy All these patients were cured of their vertigo In 9 of 15 patients (60%) whose loss of hearing exceeded 50 dB was preserved hearing postoperatively and in 4 patients there was even a certain improvement (20 dB or more for frequencies 500 1 000 and 2 000 Hz) In 2 patients reduction in hearing exceeded 10 dB In 87% tinnitus was relieved by the operation.

The results of ultrasound treatme been reported for 228 patients

postoperatively by Drettner et al. (1970) In this material the vertigo disappeared completely in 56% and was less pronounced in 33% thus the total improvement was 89% Tinnitus disappeared in 14% was less pronounced in 34% and remained unchanged in 52% Hearing, tested for frequencies 500 1 000 and 2 000 Hz, showed improvement exceeding 10 dB in 17% no improvement in 47% and deterioration in 36% of the patients.

Opening of the endolymphatic sac was introduced by Portmann in 1926 The results in 60 of his cases were studied by Boussens (1961) The immediate postoperative results showed relief from vertigo in 93% and from tinnitus in 35% The hearing damage was cured in 32% and improvement occurred in 24% Five years postoperatively 82.7% were free from vertigo

A subarachnoidal shunt operation was performed by among other investigators House (1964) He showed that in 7 operated patients 47% were free from vertigo in 29% there was postoperative improvement 11% were free from tinnitus, 40% showed improvement and in 11% improvement in hearing exceeded 20 dB for the speech frequencies.

Fick (1964) reported that Plester had opened the stapedial foot plate in 12 patients, in 50 there was freedom from vertigo, and in 25% disappearance of tinnitus. Fick himself perforated the foot-plate and the saccule with a fine needle. In 50 patients the results obtained were for periods from 1 to 42 months after operation, complete disappearance of vertigo in 86% improved hearing in 58% and total disappearance of tinnitus in 36%

House (1966) stated that in 60 patients who were operated and followed for up to 1 year after operation cryosurgery gave relief from vertigo in 70% and from tinnitus in 50 In about 70% there was no further postoperative decrease in hearing.

In cooperation with Tovi (see Fluur & Tovi, 1965) the author of this paper has developed a microscopic method for selected intracranial section of the vestibular nerve. The method involves partly a section of all the afferent vestibular fibres from the labyrinth to the central

Table I

Pat. no.	Years post operative	Bouts of vertigo	Unsteadiness	Tinnitus	Periods with increased tinnitus and nausea as previously preceding bouts of vertigo, but now without vertigo	Hearing
1	7	None	Sometimes during sudden head movements	Improved but varying	None	Stable
2	6	None	Sometimes during hard work	Improved but varying	None	Stable
3	6.5	None	None	Unchanged	None	Stable
4	6.5	None	None	Sometimes	Occasional nausea, but not tinnitus	Stable
5	[illegible]	None	None	Unchanged	None	Stable
6	6	None	None	Improved but varying	None	Stable
7	6	None	None	Improved but varying	Increased tinnitus and occasional nausea	Stable
8	6	None	None	None	None	Stable
9	5.5	None	None	Unchanged	None	Stable
10	5	None	In darkness	Improved but varying	Increased tinnitus and occasional nausea	Stable
11	5	None	None	None	None	Stable
12	4.5	None	When tired	Sometimes	Occasionally	Stable
13	3.5	None	None	None	None	Stable
14	3	None	None	None	None	Stable
15	3	None	Sometimes during hard work	Unchanged	None	Stable

Table II

Patient no.	Operation	Audiogram taken	250	500	1 000	1 500	2 000	3 000	4 000
1	1964 right	1964	55	65	65	55	55	55	60
		1971	55	75	70	65	60	70	65
		Results dB	0	−10	−5	−10	−5	−15	−5
2	1964 left	1964	55	[illegible]	60	35	30	40	35
		1968	50	60	55	50	55	65	75
		Results dB	−5	−5	−5	−15	−20	−25	−40
3	1964 right	1964	70	70	60	60	60	70	80
		1965	55	75	70	60	60	70	[illegible]
		Results dB	−15	−5	−10	0	0	0	−5
4	1964 right	1964	60	65	60	[illegible]	65	75	80
		1971	60	55	55	60	55	70	80
		Results dB	−10	−5	−5	+5	−10	+5	[illegible]
5	1965 left	1965	80	85	85	80	80	80	80
		1971	45	75	75	75	60	80	85
		Results dB	+35	−10	−10	+5	−20	[illegible]	−5
6	1965 left	1965	20	35	45	55	60	75	80
		1971	15	25	50	60	60	70	80
		Results dB	−5	+10	−5	−5	0	+5	0
7	1965 right	1965	50	55	50	40	35	35	35
		1971	55	65	70	70	70	90	90
		Results dB	−5	−10	−20	−30	−35	−55	−55
8	1965 left	1965	45	45	45	35	30	30	40
		1971	35	35	35	40	40	55	60
		Results dB	−10	−10	+10	−5	−10	−15	−20
9	1965 left	1965	40	50	25	[illegible]	25	30	35
		1971	50	50	45	50	55	60	60
		Results dB	−10	0	−20	−25	−30	−30	−25
10	1965 right	1965	60	60	55	55	50	60	65
		1971	65	65	60	60	55	70	60
		Results dB	−5	−5	−5	−5	−5	−10	+5
11	1966 right	1966	50	90	80	70	70	80	85
		1971	80	80	70	70	75	75	85
		Results dB	−30	−10	+10	0	−5	+5	[illegible]
12	1966 right	1966	45	45	50	35	25	30	35
		1971	70	65	60	60	60	60	65
		Results dB	−25	−20	−10	−25	−35	−30	−30
13	1967 left	1966	45	50	45	30	35	50	55
		1971	45	45	40	35	30	50	50
		Results dB	0	−5	+5	−5	+5	0	+5
14	1968 left	1968	50	50	35	30	30	30	30
		1971	55	50	45	40	40	45	40
		Results dB	−5	0	−10	−10	−10	−15	−10
15	1968 left	1969	75	80	[illegible]	85	80	75	75
		1971	65	80	85	85	[illegible]	80	80
		Results dB	+10	0	0	0	−5	−5	−5

nervous system, and partly a section of the efferent fibres from the central nervous system to both the cochlea and the vestibular organ. One of the hypotheses on which the operative method is based is that the efferent nerve fibres to the labyrinth influence the vascular system in the internal ear and therefore a nerve section should produce an alteration in the endolymphatic secretion or in resorption.

We used a suboccipital approach and removed about 3 × 3 cm of the bone post to the sigmoidal sinus. The dura

Table III

	Vertigo relieved	Vertigo less pronounced	Tinnitus			Hearing		
			Relieved	Improved	Unchanged	Improved	Stat.	Decreased
Labyrinth destruction	100							100
Vestibular nerve section								
Olivecrona	96							31.5
Dandy	90							
Fisch	91.9	8.1	44.4	41.7	13.9	26	60	14
Fluur	100		27	46	27		80	20
Ultrasound								
Drettner et al.	56	33	14	34	52	17	47	36
Subarachnoidal shunt operation								
House	47	29	15	40		11		
Plester	50		25					
Fick	86		36			58		
Cryosurgery								
House	70		50				70	

and the cerebellum pushed aside with a spatula so as to leave a space of about 1 cm between the posterior surface of the temporal bone and the anterior surface of the cerebellum. The internal meatus was explored and the vestibular nerve detached and divided.

At first, only patients with advanced Ménière's disease who were severely affected and found it difficult to continue working were chosen for operation, but subsequently other patients were also included, who were able to ...ctice their professions, but suffered from ... acute bouts of vertigo

... author was interested to ascertain the ...ondition of the 15 patients included in the whole material, 3 to 7 years after operation so as to study how the operation had influenced both the symptoms and the course of the original disease

RESULTS

Table I shows the postoperative frequency of the different symptoms. None of the 15 patients had had a bout of vertigo since the operation 5 patients have sometimes, but very rarely felt slight unsteadiness. Tinnitus had disappeared in 4 patients (27). In 7 patients (46%) there was improvement, b... sometimes tinnitus of varying intensity occu... red, especially during some form of stre... Consequently 73% of the material showed ... improvement in respect of tinnitus. In 4 p... tients tinnitus had remained unchanged aft... operation. Four patients had on a few occ... sions felt an increase in tinnitus and sligh... nausea, just as they had done previously b... fore a fit, but now without vertigo.

As regards hearing all the patients state... that, subjectively it was stable Table II show... the preoperative state of hearing and that ... to 7 years after operation The patients hav... had checkups every year Slight fluctuations i... the hearing were occasionally observed, some... what better or somewhat worse. However ... an average the values had remained about th... same as those reported in this material.

Here it was found that hearing naturall... showed different results for different fre... quencies, but deterioration exceeding 10 d... for all frequencies occurred in only 3 patient... In 12 patients (80%) hearing remained un... changed, on the whole, despite the fact that ... 10 of the 15 patients loss of hearing exceede... 50 dB For certain frequencies some of th... patients showed definite improvement, wherea...

for other frequencies hearing had deteriorated. Consequently no report has been given on possible improvement in postoperative hearing.

DISCUSSION

The results obtained in this material show good agreement with those of Fisch, where the same type of operation was applied even if the approaches were different. Naturally the present material is too small for a safe assessment of the reliability of the method, but taken together with the results of Fisch they give a good indication of what a patient with Ménière's disease may expect from a selective vestibular nerve section compared with other operative methods. In Table III a short survey of the different results is given, which shows that a selective nerve section gives better results than other methods as regards both the vestibular and the cochlear symptoms in Ménière's disease. The results obtained in respect of the hearing also indicate that even if a nerve section may not cure the disease, it can nevertheless, in most cases, prevent its further progress.

ZUSAMMENFASSUNG

Eine Untersuchung 3–7 Jahre nach selektivem Abschneiden von N. vestibularis in Ménières Krankheit wurde bei 15 Patienten vorgenommen, die vor der Operation schwere Anfälle von Schwindel, Tinnitus und Gehörschädigungen hatten. Die Schwindelanfälle verschwanden bei 100%. Tinnitus wurde verbessert bei 73% und blieb unverändert bei 27%. Das Gehör blieb unverändert bei 80% und wurde schlechter bei 20%. Es zeigt sich, dass ein selektives Abschneiden von N. vestibularis auf längere Zeit gesehen bessere Resultate ergibt als andere Operationsmethoden. Es deutet auch darauf hin, dass diese Operationsmethode, wenn nicht heilt, so doch in den meisten Fällen die weitere Entwicklung der Krankheit verhindert.

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RHINOSCLEROMA IN FINLAND

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Abstract The authors present the first case of rhinoscleroma in Finland. The patient was a farmer's wife aged 41 from eastern Finland. The rhinoscleroma in this case was possibly caused by *Klebsiella serratia* which could be cultured in abundance from crushed tumour tissue. *Klebsiella rhinoscleromatis* Frisch, therefore was not the causative factor in this case. Treatment consisted of suppressive doses of corticosteroid combined with Bactrim® and Terramycin® Despite an extremely good response to the treatment the case cannot be considered completely cured.

Rhinoscleroma is a chronic disease of the respiratory tract, similar in character to specific granuloma. The disease is slowly progressive and, if untreated, usually leads to asphyxia due to obstruction of the airways. Today a large number of these patients can be treated [illegible] Hebra (1970) was the first to describe the disease under the name of rhinoscleroma. Hebra & Kaposi (1870) studied the histology of the tumour and came to the conclusion that it could be referred to an intermediate category between glioma and sarcoma. Mikulicz (1877) claimed that an inflammatory process was *involved*. He also described the histology of the tissue, and the typical vacuolated cells which later came to be called the Mikulicz cells. Frisch was able in 1882 to culture from the cells themselves a bacterium, *Bact rhinoscleromatis* which he believed, and which is still believed today to be the causative factor of the disease. In 1885 Cornil & Alvarez also managed to demonstrate this bacterium in the vacuolated Mikulicz cell. Goldzieher & Neuber (1909) proved the specificity of the Frisch bacterium by demonstrating that the patient's serum agglutinated Frisch's bacteria, and gave a positive complement fixation reaction to the antigen of the scleroma. Streit (1935) stated that the Mikulicz cells found in scleroma may develop from various cells such as fibroblasts, plasma cells, histiocytes, leukocytes, and also epithelial cells. Every cell invaded by the Frisch bacterium undergoes a specific degeneration and becomes a Mikulicz cell. The formation of these cells is regarded as a defensive mechanism against the bacteria, particularly where tonicity of the organism is relatively low In 1945 New et al. reported cases of rhinoscleroma "healed" by streptomycin. Miller (1949) described the streptomycin treatment of a patient with rhinoscleroma which, however was not fully cured by this treatment. Zakrzewski & Dursla-Zakrzewska (1964) cured 70% of their cases with streptomycin and a few with terramycin.

In Europe, the disease is endemic in Ukraina, Poland and Yugoslavia, *to a limited extent* in Switzerland, and in very few cases in Germany Wolkowitsch, as early as 1889 reported 11 cases of rhinoscleroma in Russia. In France it occurs among immigrants from countries with endemic sources, but not among the domestic French (Cornil, 1883) The most important endemic foci outside Europe are in Mexico, Guatemala North Africa, and on the islands of Celebes and Sumatra. The total

number of the cases of rhinoscleroma in the whole world is estimated at 10 000–15 000 (Zakrzewski, 1965). As far as is known, only five cases have to date been published from Sweden (Welander 1887 Carlens, 1940· Handstedt, 1946 Hagqvist et al. 1966). No case of the disease elsewhere in Scandinavia is known to have been reported previously The first case from Finland is reported here.

CASE REPORT

The patient was a farmer s wife aged 41 from eastern Central Finland. She had never been abroad or in touch with a foreigner or even anybody who had spent a lengthy period abroad. Since 1961 her left nasal cavity had become narrowed and gradually blocked. Early in 1962 and at the end of 1963 tumour tissue had been removed from the left nasal cavity On both occasions a tumour the size of a thumb tip was removed from the posterior part of the inferior turbinate. The tumour surface was yellowish red, relatively soft, and showed a dense vascular network. Histologically it proved to consist of lymphatic tissue predominated by a massive hyperplasia of atypical, reticular cells and plasma cells (Fig 1) The reticular cells were swollen, either vacuolated or homogeneous, and stained feebly by the routine methods, with haematoxylin and eosin, and van Gieson. The nuclei were centrally located and relatively small, but rich in chromatin (Fig. 2) Individual giant cells, with several nuclei of the same type but with common, vacuolated or "ground-glass" type plasma could be sporadically seen. These swollen reticular cells of a very unusual type aroused the pathologist's suspicion of rhinoscleroma. Bacterial culture at this time showed that Klebsiella bacteria of a type not defined in detail grew in the nasal mucosa. This bacterium in vitro, revealed a high degree of sensitivity to sulfa (+ + +) and a relatively high sensitivity to streptomycin and chloramphenicol (+ +)

A relapse was noted as early as 6 months after the second operation, and 2 years later by 1965 the tumour had spread to the left maxillary sinus, the ethmoid sinus and both sphenoid sinuses. A major operation was performed in 1965 During the patient s stay in the hospital, a course of 20 g streptomycin was given. Postoperatively the patient remained symptom-free until 1968 when a relapse was again noted. The same year the lymph nodes of the neck were seen to be swollen bilaterally and they grew gradually until they reached the size of an egg (Fig. 3).

A biopsy specimen of the swollen lymph nodes showed chronic inflammation. The atypical, reticular hypertrophic cells with vacuolated cytoplasm were seen in varying numbers, locally forming very dense aggregates but without sharp contours (Figs. 4 5). The patient began to complain of respiratory distress in the spring of 1969 Roentgenology revealed a bilateral compression of the trachea, and expansion of the upper mediastinum apparently as a result of lymph node swelling. From April to September 1969 the patient was given 1 g streptomycin a day a total of 130 g, without any noticeable effect on the disease. From December 1969 to September 1970 she was given 10–15 mg Nurison® daily and 500 mg Tetracyclin® twice daily without any appreciable effect on the disease except that the swelling of the neck decreased slightly

In October 1970 the patient was admitted to the Department of Otolaryngology Helsinki University Central Hospital. Her left nasal cavity was filled by a reddish tumour with smooth surface. The tumour pressed against the septum dislocating it, with the result that the right nasal cavity also was blocked The tumour protruded from the left nostril Lymph node accumulations the size of a fist were seen on both sides of the neck. A biopsy specimen of the nasal cavity tumour was taken and bacterial culture was made on crushed tumour tissue. The bacterium found abundantly was *Klebsiella serratia*. Corticotherapy and treatment with Bactrim® stituted The initial cortisone dosage,

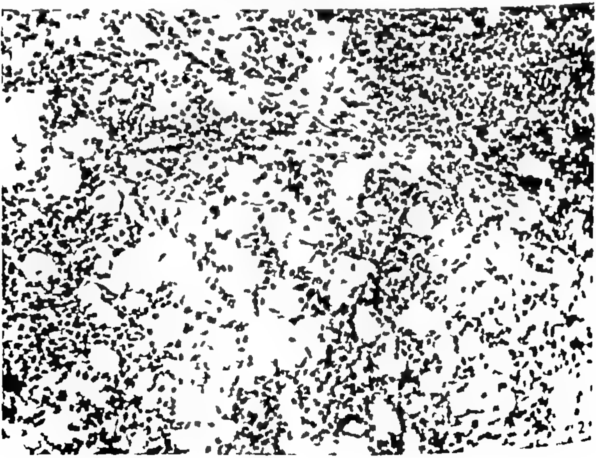


Fig. 3 Photograph showing the swolle of the neck.

routinely used by this clinic for the treatment of Wegener's granulomatosis (Grahne & Zechner 1966) i.e. Prednison® with 16 tablets of 5 mg each daily

Initially the treatment proved to be highly effective. In 3 weeks the patient's sedimentation rate fell from 112 to 13 mm h. The dosage of corticosteroids was reduced gradually at a few day's intervals, to 15 mg Prednison® per 24 hours. When the patient after 5 weeks in the hospital was discharged for outpatient treatment, she first took 15 mg Prednison® daily until the dose 1 month later was reduced to 10 mg every 2 days. The patient was treated with corticosteroids and Bactrim® for a total of 4 months. During the last 6 weeks of treatment the pathological process in the left nasal cavity and on both sides of the neck remained unchanged. Although the tumour process in the nose and on the neck has clinically almost disappeared the disease can be histologically demonstrated at these sites.

DISCUSSION

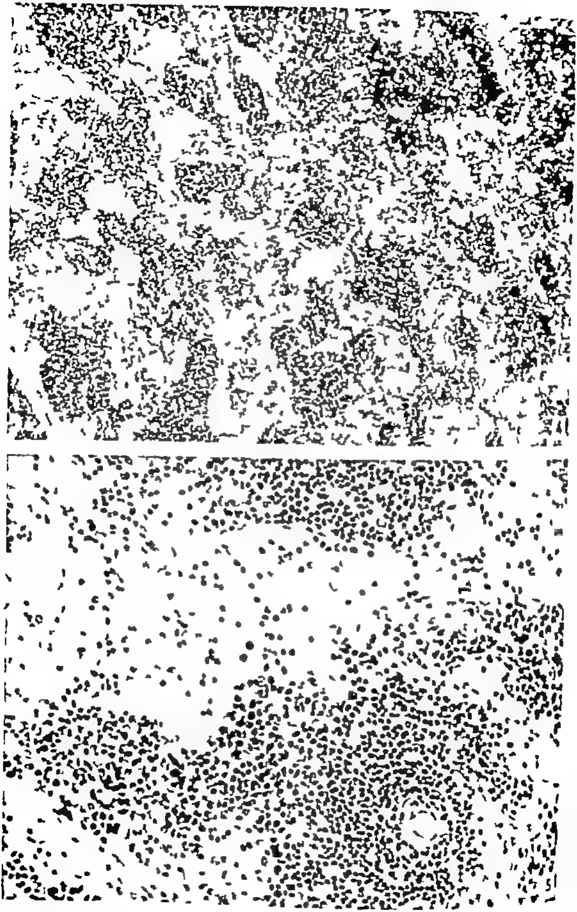
Szmurlo (1933) described different stages in the development of the disease and concludes that the first stage is atrophic rhinitis with crust formation, in other words, ozaena. Ozaena would be the result of a chronic infection in the upper respiratory tract, and would then develop into an exudate-producing and finally a sclerosing stage. Cases of ozaena are fairly common in Finland, yet it is never seen to develop into rhinoscleroma. Nor was there any indication in the reported case to suggest that the disease might have begun as ozaena.

A very interesting finding is that the Klebsiella bacterium found abundantly in the crushed tumour tissue was not of the Frisch type but a *Klebsiella serratia*. Possibly the disease in this case had been caused by just this bacterium. Nor had the patient been in touch with anybody who could have infected her with Frisch klebsiella.

Hencner (1967) described in his work 54 clinically diagnosed cases of rhinoscleroma a *Kl. rhinoscleromatis* strain was cultured bacteriologically from 37 of them. In his serologic studies he obtained a positive antibody response in 51 cases, with titres ranging 1 5–25 600. The methods used in the studies of this particular case were the complement fixation test, agglutination test, and demonstration of incomplete antibodies with Coombs

Fig. 1 Photomicrograph of rhinoscleroma tissue from nasal mucosa. Swollen reticular Mikulicz cells form the majority of the tumorous granulation tissue. Among and between them the smaller cells are mainly lymph cells and plasma cells. Hematoxyl × 80.

Fig. 2 Photomicrograph showing the sw lar Mikulicz cells in the granulomatous nasal mucosa. Hematoxylin-eosin, ×



technique. In all tests, the antigen had been prepared from a strain of *Kl rhinoscleromatis* (5046, Copenhagen I. Orskov) The serum of the present patient taken Oct. 20 1969 and kept deep-frozen at −20 C until examined, was titrated with the same Copenhagen strain and parallel also with *Kl. ozaenae* (5050 Copenhagen), using corresponding methods, but no positive reaction could be shown in any of the tests. The test series was repeated on the same specimen after a couple of months, again with negative results.

The final treatment in the form of a supp es sive dose of corticosteroid, and with Bact m® and Terramycin® gave a very rapid response The tumour accumulations on the neck almost completely disappeared, and the blocked nose was again free for respiration This notwithstanding, the patient cannot be considered completely cured. Some tumour tissue remains in the nasal cavity and on the neck

ZUSAMMENFASSUNG

Die Autoren beschreiben den ersten Fall von Rhinosklerom in Finnland. Die Patientin war die 41-jährige Ehefrau eines Landwirts aus Ostfinnland Das Rhinosklerom war in diesem Falle möglicherweise on Klebsiella serratia verursacht worden Diese Bakterien konnten in großen Mengen auf dem zerriebenen To morgewebe kultiviert werden Klebsiella rhinoscleromatis Frisch war in diesem Falle so nicht Urheber der Krankheit. Die Behandlung bestand in suppressiven Dosen von Kortikosteroiden kombiniert mit Bactrim® und Terramycin® Obwohl der Fall ausgezeichnet auf die Behandlung reagierte, kann die Patientin doch nicht als völlig geheilt gelten.

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Fig 4 Photomicrograph of a lymph node specimen on the neck showing broad sinuses with massive hyper plasia of the reticular cells of Mikulicz cell type Hematoxylin-eosin, 80.

Fig 5 A higher magnification of the node specimen as in Fig 3 The two licz cells are filling the broad sinuses. usually small germ centres is seen toxylin-eosin. 250

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PRE IRRADIATION QUALITIES OF A PAROTID GLAND PREDICTING THE GRADE OF FUNCTIONAL DISTURBANCE BY RADIOTHERAPY

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Abstract In the irradiation of head and neck tumours, often more than one of the major salivary glands and also many of the minor salivary glands are located within the therapy beams. This might then explain any functional disturbance of the salivary gland tissue causing xerostomia with difficulties in swallowing, a high incidence of caries, etc., after radiotherapy in this region. As the grade of these complications shows a great interindividual variation, it is questioned whether there is an individual sensitivity to irradiation therapy of the salivary gland tissue. To ascertain whether it is possible to predict in which patients radiotherapy will be more liable to cause a functional disturbance, a study has been made of 15 parotid glands located within the therapy beams at radiotherapy of malignant head and neck tumours to find whether any correlation exists between the pre [illegible]ation quality of the glands and their reaction to [illegible]ion at different doses. The pre-irradiation [illegible]lity of the parotid glands has been studied by sialo- [illegible] and sialometry and their function during the irradiation period by sialometry during stimulation of the secretion rate with 1% citric acid. The present study shows so great an interindividual variation in the decrease of the stimulated secretion rate at irradiation that it seems impossible to estimate a definite critical dose level for extinction of parotid glands. It has, however also been shown that the pre-irradiation qualities of the parotid glands provide valuable information about the individual reaction of the parotid glands to irradiation. These findings are important for determining the risk of complications in the mouth and throat by radiotherapy of malignant tumours in the head and neck region.

Parotid glands are often located within the therapy beams during radiotherapy of malignant tumours in the head and neck region A reduction of the size of the parotid glands as well as a decrease in the salivary secretion rate have been demonstrated one year or more after the end of the irradiation period (Eneroth et al. 1971) The salivary secretion rate was, however very low even just at the end of the irradiation period. Thus a functional disturbance must have occurred during the course of radiotherapy For this reason Eneroth et al. (in press) also studied the function of parotid glands during fractionated irradiation therapy and found that there was a wide individual variation of the irradiation doses which caused a pathological decrease in the salivary secretion rate

In the irradiation of head and neck tumours often more than one of the major salivary glands and also many of the minor salivary glands are located within the therapy beams. If the functional disturbances of these glands are sufficiently pronounced the irradiation therapy will be more or less complicated by dryness of the mouth and throat, an increased frequency of caries and often difficulties in swallowing. In planning of the radiotherapy of malignant tumours of the head and neck region these complications should be considered

It would therefore be of great interest to know whether there is an individual variation in sensitivity to irradiation therapy [illegible]

Table I. *Sex, age and diagnosis of the eleven individuals undergoing radiation therapy*

Number of patient	Number of parotid gland	Sex	Age	Diagnosis
1	1 and 2	♂	45	Nasopharyngeal carcinoma
2	3 and 4	♂	53	Nasopharyngeal carcinoma
3	5 and 6	♂	57	Nasopharyngeal carcinoma
4	7 and 8	♂	66	Nasopharyngeal carcinoma
5	9	♂	50	Carcinoma of the gingiva
6	10	♂	50	Carcinoma of the tongue
7	11	♂	58	Carcinoma of the tonsil
8	12	♀	61	Carcinoma of the tonsil
9	13	♂	64	Carcinoma of the tonsil
10	14	♂	74	Carcinoma of the gingiva
11	15	♂	54	Sarcoma of the tonsil

salivary gland tissue. If so, it would perhaps be possible to predict in which patients the radiotherapy will be more liable to cause functional disturbances of the salivary glands.

The purpose of the present study was to record the doses which practically eliminate the function of a parotid gland and to study whether there is a correlation between any pre-irradiation quality of a parotid gland and the reaction in different irradiation doses.

MATERIAL

The material consists of 15 parotid glands of 11 individuals undergoing radiation therapy for tumours in the region of the head and neck. The sex and age at the time of treatment and the diagnosis of the tumours are given in Table I. There was no history of pathological salivary conditions of the parotid glands, but two patients had sometimes a subjective sense of a slight dryness of the mouth (patients 1 and 8). The patients were treated with the Siemens Gammatron I Cobalt-60 unit, giving a dose rate of 40–65 rad/min, or with the Varian linear accelerator operating at 60 mV and with dose rate of 200–250 rad/min. The parotid gland dose was calculated from the physical dose planned for each patient. All patients received fractionated radiotherapy with a daily tumour dose of 200–250 rad. A total dose of 4 000–7 200 rad was given to the parotid glands with an overall treatment time of 4 to 8 weeks. In four patients (nos. 1–4) both parotid glands of the patient were situated within the therapy beams. In seven patients (nos. 5–11) one parotid gland was situated within the therapy beams. In these cases (nos. 5–11) the parotid gland on the non-tumour side received a dose less than 10% compared with the parotid gland on the tumour side.

The patients were examined by sialometry before and during the period of radiation therapy. Sialography was performed before irradiation in all patients.

METHODS

Sialography is the radiological demonstration of the ductal system of the salivary glands after the injection of contrast medium into excretory ducts. An apparatus for skull radiography is used (Elema-Schönander CRT 4) for this examination. The injection of the contrast medium is given manually at a slow rate from a syringe. The contrast medium used is 60% Urografin. The central ray is directed towards the midpoint of the gland and inclined caudally at an angle of 18 degrees to the vertical plane (Fig. 1). Three sialograms are exposed, the first when the patient signals that he feels a

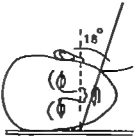

Fig. 1. The orientation of the skull the beam in lateral projection.

sense of tension, the second and third when he signals slight pain. The three sialograms were exposed at 0 and at +3 and −3 in the ventral and dorsal directions respectively Five minutes after the contrast injection a film was exposed in order to check the disappearance of the contrast medium

In the assessment of the sialograms there are three main factors of interest. the appearance and frequency of the ducts, the projected areas of the parotid gland and the time of disappearance of the contrast medium. The area of the gland in the sialograms is traced and there after determined planimetrically All values of the single parotid glands are means of two separate determinations on the two sialograms best filled by contrast medium in each case. The measurements were performed with a planimeter Ingut 9544-11 type OTT

The *sialometric method* is a modification of the method described by Lashley (1916) Enfors (1962) and Ericson (1968) During the secretory determinations the patient reclined

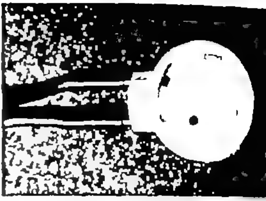

Fig 2 (a) Photo of the collecting and suction cu

in a dental chair with the sagittal plane ver cally The recordings were made during re and during stimulation with 1% citric ac The citric acid was applied to the midline the anterior third of the dorsum of the tong three drops every 30 sec. The patient was i structed to move her tongue after every i stillation and to swallow between instillation

The saliva was collected with a plastic c over the orifice of Stenson s duct. Th c

Fig (b) Photo of th m tion cup the polyeth e tubes and, to the right, the plastic container To th left the uction balloon

Fig. 3. Photo of a patient undergoing sialometry of the parotid glands.

lecting cup was connected to a small plastic container by means of a polyethylene tube (Fig. 2 *a*, *b*). Outside the collecting cup a circular suction cup held the collecting cup tightly to the cheek. The recordings were made simultaneously on the left and right sides during 10-min periods (Fig. 3). Before and after the recordings the collecting cup, polyethylene tube and plastic container were weighed while enclosed in a plastic box.

The secretion of the parotid glands was recorded until the gland produced less than 600 mg, i.e. ten drops per 10 min at 1% citric acid stimulation. This value corresponds to one-tenth of the mean value of a control material of 184 parotid glands given by Ericson, 1968. From a practical point of view it might be considered that a parotid gland with such a low stimulated secretion rate would have been extinguished by the irradiation.

The resting and stimulated secretion rates were recorded at dose levels of 550–700, 1 000–1 400, 1 600–2 000, 2 600–3 000 and 3 600–4 200 rad. For various reasons not all glands could be examined at all the dose levels mentioned.

ERRORS OF THE METHODS

Sialography

The sialographic findings obtained at examination prior to radiation therapy include an evaluation of the projected area of the parotid glands. The errors of measurement of the area on the sialograms are referable both to the planimetric procedure and to the quality of the sialogram. The quality of the sialogram depends on the projection, the exposure, and on the grade of contrast filling. The error of the planimetric procedure was determined by double determinations and the precision, as expressed by the standard deviation for a single determination, was 0.11 cm². The area was also measured on two sialograms of each gland, the two sialograms being exposed at an angular difference of 6°. The standard deviation for a single determination was 0.78 cm².

Sialometry

Sialometry comprises resting secretion and 1% citric acid stimulated secretion and was performed for each subject at the same time of the day and at least 1 hour after eating or drinking. A collection time of 10 min should suffice (Bertram, 1967). The technical handling of the suction collecting cups and the weighing procedure are easy for a trained person and the error due to these procedures should be small compared with the interindividual variation. In order to ascertain the intra-individual variation of the stimulated secretion of the parotid gland, double determinations were performed for eight glands (nos. 1, 2, 3, 4, 7, 8, 14 and 15). The recordi
were repeated on two subsequent days
the start of the radiation therapy
standard deviation for a single det
was 660 mg per 10 min. The mean
stimulated secretion was 3 730

Table II *Projected area of parotid glands occurrence of changes in calibre of main duct sialodochiectasis and retarded disappearance of contrast medium*

The area of glands . and 4 was not measurable

Number of parotid gland	Area of the parotid gland (cm²)	Findings in the sialograms: Changes in calibre of main duct	Sialo-dochiectasis	Retarded disappearance of contrast medium
1	14.5			
2	—			
3	19 7			
4	—			
5	16 0			
6	22.0			
7	18.9			
8	18.6			
9	13.3			
10	20.3			
11	.3.6			
1	19.0			
13	19 7			
14	15.5			
15	15.3			
n	13	Moderate changes	< 1 mm diameter	Contrast medium in
Mean	18.2			the duct
S.D	3.03	Pronounced changes	1–2 mm diameter	after 5 min
S.E.	0 84			

for the glands mentioned. As the irradiation occurred every day no double determination was performed during the period of the radiation therapy

RESULTS

...lography

The sialographic findings obtained prior to radiation therapy are given in Table II The area of the glands has a mean value of 18.2 cm² (S.D 3 03 cm² and S.E. 0 84 cm²) with range 13 3 cm² to 23 6 cm² The median value was 18.9 cm²

From Table II it appears that five parotid glands (nos. 3 4 5 6 and 10) show changes in the calibre of the main duct and two (nos. 5 and 6) also have strictures. In four glands (nos. 3 4 ■ and 11) sialodochiectasis is seen. Glands which have a projected area on the sialogram of more than 20 cm² exhibit changes in calibre of the main duct and or sialodochiectasis (glands 6 10 and 11). In two cases (glands 1 and 12) the contrast medium had not disappeared 5 min after the injection, indicating a low secretion capacity (Rubin & Holt, 1957)

Sialometry

In Table III are presented the individual values, the mean values, the standard deviations and the standard errors for the resting and 1 % citric acid stimulated secretion as measured before the radiation therapy It will be seen that the variation between the glands examined is very large

Resting secretion during the period of irradiation

During the period of irradiation secretion decreases successively Table IV a shows the mean values, the standard deviations, the standard errors, the median values and the ranges for the resting secretion of parotid glands 1–8 at the different dose levels The eight glands mentioned are the left and right parotid glands of patients 1–4 who were ...

Table III *Individual values, mean values, standard deviations (S.D) and standard errors (S.E.) for resting and 1 % citric acid stimulated secretion before radiation therapy*

Number of parotid gland	Secretion before irradiation, in mg/10 min: Resting secr	1 % citric acid stim. secr
1	10	990
2	70	1 300
3	220	1 760
4	110	3 770
5	.110	.170
6	1 730	3 180
7	250	1 090
8	20	3 300
9	1 390	.700
10	67?	1 870
11	.980	8 ?40
12	40	510
13	370	4 040
14	?90	820
15	60	.340
n	15	15
Mean	700	3 530
S.D	910	3 120
S.E.	40	810

Table IV *a* and *b* *Mean values, standard deviations (S.D) standard errors (S.E), median values and ranges for resting secretion in (a) parotid glands 1–8 and (b) parotid glands 9–15 at different levels of irradiation*

	Resting secretion in mg/10 min					
		During the period of irradiation (doses in rad)				
	Before irradiation	550–700	1 000–1 400	1 600–2 000	2 600–3 000	3 600–4 200
IV *a* Glands 1–8						
n	8	8	8	5	5	—
Mean value	570	120	90	20	40	—
S.D	850	220	190	10	30	—
S.E.	300	80	60	10	10	—
Median value	170	40	20	20	20	—
Range	10–2 110	0–650	0–520	0–40	20–80	—
IV *b* Glands 9–15						
n	7	7	6	7	7	7
Mean value	850	70	150	120	100	20
S.D	1 030	100	330	190	100	10
S.E.	390	40	140	70	40	3
Median value	370	30	10	50	60	20
Range	50–2 980	10–300	10–830	10–540	0–300	10–30

radiated bilaterally in the region of the parotid glands. In Table IV*b* the corresponding data are given for the unilaterally irradiated parotid glands 9–15 It can be seen from Tables IV *a* and *b* that there is a marked decrease of the mean value of the resting secretion after a dose of 550–700 rad.

The individual values for the resting secretion are very low less than 60 mg (1 drop) per 10 min, for eleven glands measured at dose levels of 550–700 rad and for four glands (nos. 5 7 10 and 11) measured at dose levels of 1 000–4 200 rad.

Stimulated secretion during the period of irradiation

In Tables V *a* and *b* are given data corresponding to those in Tables IV *a* and *b* and it is seen that the decrease of the stimulated secretion values has a very large interindividual variation. The maximum variation is graphically illustrated for four parotid glands in Fig. 4 Glands 1 and 15 represent the glands with lower pre-irradiation secretion values than the mean value of the fifteen glands. For these two glands the stimulated secretion rate is less than 600 mg per 10 min (practically extinguished according to our definition) at a dose of 550–700 rad. Practically the same strength of reaction exists in five other glands (nos. 2, 3 6, 9 and 12) at the same dose of irradiation

On the other hand the two parotid glands

Table V *a* and *b* *Mean values, standard deviations (S.D), standard errors (S.E.), median values and ranges for 1 % citric acid stimulated secretion in (a) parotid glands 1–8 and in (b) parotid glands 9–15 at different levels of irradiation*

	1 per cent citric acid stimulated secretion in mg/10 min					
		During the period of irradiation (doses in rad)				
	Before irradiation	550–700	1 000–1 400	1 600–2 000	2 600–3 000	3 600–4 200
V *a* Glands 1–8						
n	8	8	8	5	5	—
Mean value	2 180	850	820	290	230	—
S.D	1 090	1 230	870	240	280	—
S.E.	380	440	310	110	130	—
Median value	1 940	350	570	180	320	—
Range	980–3 720	40–3 810	0–2 230	20–560	20–600	—
V *b* Glands 9–15						
n	7	7	6	7	7	7
Mean value	5 080	2 600	1 040	2 020	1 320	
S.D	4 020	3 870	1 650	2 850	2 510	
S.E.	1 520	1 460	670	1 080		
Median value	2 820	1 280	152	460		
Range	2 340–1 870	10–10 820	10–4 100	7 5		

Table VI Mean values, standard deviations (S.D) and standard errors (S E) for 1 citric acid stimulated secretion in the parotid glands on the non-tumour side of patients 5–11 before the irradiation period and at doses of approx 60 and 400 rad

	1 per cent citric acid stimulated secretion in mg 10 min		
	Before irradiation	During the period of "irradiation" (doses in rad)	
		55–70	360–420
n	7	7	7
Mean value	4 540	5 160	4 360
S.D	3 170	4 370	3 510
S.E.	1 180	1 650	1 330

(nos. 10 and 11 in Fig. 4) which have the highest preirradiation secretion values are extinguished at a much higher irradiation dose. The secretion values are diminished below the level of extinction (600 mg per 10 min) at a dose of 3 800 and 4 200 rad respectively The remaining six parotid glands (glands 4 5 7 8 13 and 14) are extinguished at irradiation doses of 1 000–2 800 rad

The individual reaction of the parotid glands to irradiation might be expressed as the relative decrease of the stimulated secretion rate during the period of irradiation. The relative decrease can be expressed as the ratio of the stimulated secretion rate at a certain dose level and the pre irradiation stimulated secretion rate. The relative decrease is determined three dose levels 550 00 rad, 1 000–1 400 ad and at 1 600–2 000 rad The interindividual variation of the relative decrease of the stimulated secretion rate wa very large.

It is of interest however to investigate whether there is any connection between the relative decrease of th stimulated secretion rate and the pre-irradiation secretion rate because this secretion rat may be assumed to be an expression of the pre-irradiation quality For each dose level mentioned a correlation analysis has been performed between the relative decrease of the secretion rate and the pre irradiation stimulated secretion of all 15 parotid glands.

The analysis shows that parotid gland w h high pre-irradiation secretion rate have a smaller relative decrease than those with low pre irradiation secretion rate The correlations are of such a magnitude (r 0 63 r 0 52 a d $r = 0.72$ for each dose level) as to be probab y significant ($p < 0.05$).

In cases undergoing radiation therapy unilaterally (patients 5–11) the parotid gla d on the opposite side receive a dose less than 10 compared with the parotid glands within th therapy beams. The secretions of both par d glands in the unilaterally irradiated pa en s 5–11 were recorded simultaneously In Ta VI are presented the mean values, sta da d deviations and standard errors of th 1 citric acid stimulated secretion of the parotid glands on the non tumour side of patients 5 11 on three occasions: before the radiation ther apy and at doses of 550–700 and 3 600–4 00 rad on the tumour side respectively Thus the doses to the parotid gland on the non-tumour side in these patients might be as high as 55–70 and 360–420 rad respectively on the tw latter occasions. Table VI indicates that, d ing the period of irradiation, the p d glands on the non-tumour sid still prod approximately the same amount of saliva ing 1 citric acid stimulation.

The subjective reaction of dryness o t mouth xerostomia, differs greatly between patients who were bilaterally (nos 1–4) a those who were unilaterally (nos 5–11) radiated. Patients 1–4 complained of xerostomia after a dose less than 2 000 rad, wher as patients 5–11 did not suffer from xeros with one exception patient 8 who compla of xerostomia even before the irrad ation. Th sialograms of the parotid glands of this pa obtained before the irradiation, showed a retarded disappearance of the contrast med indicating a low secretion capacity

DISCUSSION

The purpose of the present study was to in vestigate whether there is a correla on be

tween any pre-irradiation qualities of a parotid gland and the grade of functional disturbance of the same gland by irradiation therapy. From the therapeutical point of view it would be of great interest to be able to predict an individual sensitivity of parotid glands to radiotherapy as functional disturbances of salivary glands may be followed by more or less troublesome complications from the mouth and throat.

The pre-irradiation quality of the parotid glands has been studied by sialography and sialometry and the function during the irradiation period by gustatory stimulation of the secretion rate with 1 % citric acid. As cholinergic stimulation with intravenous injection of betacholyl was inconvenient with such frequent recordings, and as many of the patients complained about a smarting pain at 6% citric acid stimulation we have used 1% citric acid to stimulate the secretion in all cases. The bilaterally irradiated patients 1–4 complained of xerostomia and had a more or less pronounced subjective disturbance of the taste, as did, to a lesser extent, a few of the unilaterally irradiated patients, nos. 5–11. According to Ericson (1971) 1% citric acid gave a taste sensation in all the 92 patients in his control material. As patients 1–4 had a subjective disturbance of the taste, it is possible that the irradiation had more or less damaged the taste receptors. Therefore the stimulated secretion rate in these patients was perhaps not quite representative of the state of the irradiated parotid glands. In the unilaterally irradiated patients, nos. 5–11 however the 1% citric acid stimulated secretion rate should reflect the state of the parotid glands, even if the radiotherapy might have damaged the taste receptors on the irradiation side. This is also supported by a study by Wiberg (1971), who stated that a unilateral disturbance of the taste does not influence the function of the submandibular gland on the same side with the method of applying citric acid to the tongue used in the present study.

The sialographic finding as concerns the pro-

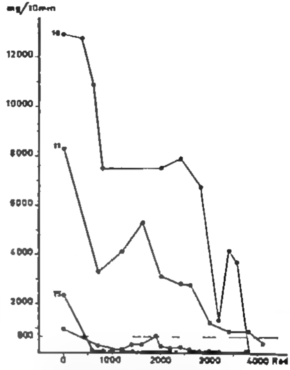

Fig. 4. One per cent citric acid stimulated secretion (mg/10 min) of parotid glands 1, 10, 11 and 15 at different doses. Curves 1 and 15 represent the gland extinguished at the smallest doses and curves 10 and 11 the glands extinguished at the highest doses. (The observations for these four patients were made more frequently than for the remaining material.)

jected area of the parotid gland is a good criterion of the secretory capacity (Ericson 1968). A retarded disappearance of the contrast medium injected is, according to Rubin & Holt (1957) a good indicator of a low secretion rate and normal glands have emptied within 5 min if the contrast is properly injected.

In the present series there were only three parotid glands with an area larger than 20 cm² among which glands 10 and 11. The size of these glands (Table II) and the stimulated secretion (Fig. 4) before radiotherapy exceeded the mean values described by Ericson.

Parotid glands 1 and 15 in Fig. 4 are, according to Table II, the smallest, with the of gland 9. Gland 1, furthermore, is two glands in the present series irradiation retarded dis

trast medium (Table II). The pre irradiation stimulated secretion rate was lowest in the present series in patient 1 and patient 15 as well had a lower pre irradiation value than the mean value of the stimulated secretion of all parotid glands examined.

From Fig. 4 it is seen that the relatively large parotid glands 10 and 11 which had the highest pre-irradiation values of stimulated secretion (the best function) were extinguished at much higher doses than the relatively small parotid glands 1 and 15 which had the lowest pre irradiation values.

In the present study the decrease of the gustatory stimulated secretion rate at irradiation varied interindividually so much that it seems impossible to estimate a definite critical dose level for extinction of parotid glands.

In the parotid glands which were practically extinguished already at a dose of approximately 550–700 rad (glands 1 2, 3, 6, 9 12 and 15) all pre-irradiation values were lower (see Table III) than the mean value of the stimulated secretion of all parotid glands examined The parotid glands which were extinguished only after much higher doses of irradiation (glands 10 11 and 13) had the highest pre-irradiation secretion value. Even if the material might be too small for universal conclusions, a correlation analysis between the pre-irradiation secretion rate and the relative decrease of the secretion rate at different irradiation doses demonstrates that the parotid glands with high pre-irradiation capacity were less sensitive to irradiation than the glands with low pre-irradiation capacity

ZUSAMMENFASSUNG

Bei der Bestrahlung von Kopf und Halstumoren liegt oft mehr als eine der grossen Speicheldrüsen und viele der kleinen intraoralen Speicheldrüsen im Gang des Strahlenbündels. Darin könnte die Erklärung für die funktionellen Störungen des Speicheldrüsengewebes liegen, die sich in Xerostomie mit Schluckbeschwerden, häufigem Auftreten von Karies usw. nach Bestrahlungsbehandlung dieses Bereiches äussern. Da der Grad dieser Komplikationen eine grosse interindividuelle Variation zeigt, ist es die Frage, wieweit eine unterschiedliche individuelle Empfindlichkeit auf die Bestrahlungstherapie des Speicheldrüsengewebes vorliegt.

Um zu sehen, ob es möglich ist vorauszusagen bei welchen Patienten in erhöhtem Masse bei einer Bestrahlungsbehandlung die Gefahr einer funktionellen Störung besteht, wurde eine Untersuchung an 15 Parotisdrüsen durchgeführt, die bei der Bestrahlungsbehandlung von malignen Kopf- und Halstumoren im direkten Strahlengang lagen. Man wollte feststellen, ob eine Korrelation zwischen dem Funktionszustand der Drüsen vor der Bestrahlung und ihrer Reaktion auf die in unterschiedlichen Dosen gegebene Bestrahlung vorliegt.

Der Funktionszustand der Parotisdrüsen vor der Bestrahlung wurde mit Hilfe von Sialographie und Sialometrie untersucht und ihre Funktion während der Bestrahlungsperiode sialometrisch unter Stimulation der Sekretion mit 1 %iger Zitronensäure verfolgt.

Als Ergebnis zeigte sich eine grosse interindividuelle Variation in der Abnahme der stimulierten Sekretmenge bei Bestrahlung, so dass es unmöglich zu sein scheint, eine bestimmte kritische Dosierungsgrenze für eine Extinktion der Funktion der Parotisdrüsen anzugeben. Andererseits konnte jedoch gezeigt werden, dass der Funktionszustand der Parotisdrüsen vor der Bestrahlung eine wertvolle Information über die individuelle Reaktion der Parotisdrüsen auf die Bestrahlung ausmacht. Diese Befunde sind ein wichtiger Faktor bei der Abschätzung des Risikos für Komplikationen im Mund und Rachen bei Bestrahlungsbehandlung von malignen Tumoren in der Kopf- und Halsgegend.

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COMPLICATIONS OF ACUTE AND CHRONIC OTITIS MEDIA IN THE ANTIBIOTIC ERA

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Abstract Ninety-six cases of complications of acute and chronic otitis media are reported. The complications were caused by acute otitis media in 43 cases and by chronic otitis media in 53 cases. Intracranial complications were present in 29 cases: epidural or perisinuous abscess in 8 cases, lateral sinus thrombosis in 5 cases, meningitis in 14 cases and temporal lobe abscess in 2 cases. All cases were treated surgically and all patients recovered.

Antibiotics and chemotherapeutics have greatly reduced the incidence of complications as well as the mortality rate of acute otitis media. In the Scandinavian countries, according to Ojala & Siirala (1953) the incidence of complications had been reduced by 73% and the mortality rate by 86.4% According to Courville (1955) the mortality of otorhinogenic complications has been reduced by 90% in the antibiotic era.

However complications of acute and chronic otitis media still occur and judging from numerous reports in the literature of the subject they are still far from harmless.

This paper is a report of 96 consecutive cases of complications of acute and chronic otitis media, treated at the ENT Department of Vasa Central Hospital during the years 1956–1971 The hospital district, having about 160 000 inhabitants, had not had any facilities for specialist treatment of oto-rhino-laryngological diseases prior to the opening of the hospital in May 1956. Chronic otitis media was, and still is a rather common disease in this area. A survey carried out in 1954 in this area among about one thousand young men, 19 years old, revealed chronic otitis media in 2.72% of those examined (Juselius, 1962).

PRESENT SERIES

Table I shows the annual number of admissions to the ENT Department and the annual number of various operations for acute or chronic otitis media and its sequelae during the years 1956–1971

As is seen from Table I, there has been only a slow decrease in the annual number of radical or modified radical operations of the middle ear There are still many cases of chronic otitis media on the waiting list.

Table II shows the annual incidence of cases with complications of acute or chronic otitis during the years 1956–1971

As is seen from Table II there has been only one complication of acute otitis media during the last 5 years.

The various complications of acute and chronic otitis media in 96 cases are shown in Table III. All patients were treated surgically and all of them recovered. The worst lasting disability in the series was total deafness in one case

Many cases of complicated ear disease were associated with more than one complicati thus accounting for a total of 150 c

Table I. Annual number of admissions and annual numbers of various operations for acute or chronic otitis media 1956–1971

Year	No. of admissions	Simple mastoid-ectomies	Radical or modified radical mastoid-ectomies	Tympano-plasties, myringo-plasties
1956	191	1	13	3
1957	371	4	44	32
1958	576	9	81	35
1959	576	10	54	6
1960	632	10	55	18
1961	387	10	35	11
1962	910	7	95	13
1963	987	16	74	5
1964	802	8	73	14
1965	1 250	6	45	30
1966	1 236	1	39	13
1967	1 290	2	33	34
1968	1 704	2	37	18
1969	1 234		31	35
1970	1 337	3	[illegible]	43
1971	1 245	3	18	47
Total	14 578	94	703	372

Table III. Complications of acute or chronic otitis media in 96 cases

Acute otitis media		
Mastoiditis		[illegible]
Mastoiditis, facial paralysis		3
Mastoiditis, serous labyrinthitis		1
Intracranial complications		
Epidural or perisinuous abscess	3	
Lateral sinus thrombosis	4	
Meningitis	9	
	14	14
		41
Chronic otitis media		
Facial paralysis		
Labyrinthine fistula with or without serous labyrinthitis		36
Intracranial complications		
Epidural or perisinuous abscess	5	
Lateral sinus thrombosis	3	
Labyrinthogenic meningitis	5	
Temporal lobe abscess		
	13	15
		53
Total		

tions in 96 cases. A list of all complications observed is given in Table IV.

The CSF findings of cases with meningitis are shown in Table V which shows that there were 7 cases of pneumococcic meningitis caused by acute otitis media.

The age distribution is shown in Table VI. As acute otitis media occurs most frequently childhood and adolescence, the incidence of mplications is accordingly most frequent in he first two decades of life. This finding is in agreement with the observations Palva & Pulkkinen (1959).

DISCUSSION

Our experience indicates that acute otitis media should still be considered a potentially dangerous disease which even in the antibiotic era may give rise to serious complications. The incidence of complications of acute otitis media, when treated by myringotomy and antibiotics appears to be rather low. According to Palva & Pulkkinen (1959) and Paavolainen (1967) the incidence of complications was only 0.43 and 0.19 respectively in cases of acute otitis media treated by myringotomy and antibiotics. It has been maintained that antibiotics alone would suffice for the treatment of acute otitis media and myringotomy has been considered unnecessary by some authors (McKenzie 1958, Dixon 1958, Derlacki 1963). On the other hand, many authors have pointed out the importance of myringotomy with regard to preventing complications and restoring the hearing as well (Davison 1955, Goodale

Table II. Annual incidence of cases with complications of acute or chronic otitis media 1956–1971

Year	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971
Acute o. m.	1	4	6	6	5	5	1	–	4	7	1	—	1	—	—	—
Chronic o. m.	1	3	7	7	4	7	1	5	—	7	3	1			—	3
Totals		7	13	13	9	1	–	7	4	14	4	1	3		—	3

Table IV *Total number of complications observed in 96 patients with complicated acute or chronic otitis media*

Acute mastoiditis	42
Facial paralysis	6
Subperiosteal abscess	14
Suppurative labyrinthitis	6
Serous labyrinthitis	3
Labyrinthine fistula	42
Epidural or perisinuous abscess	16
Meningitis	19
Brain abscess	2
Total	150

& Montgomery 1955 Hara, 1956 Palva & Pulkkinen, 1959 Siirala, 1963). Our experience too speaks in favour of early myringotomy in the treatment of acute otitis media. During the years 1956–1971 we have observed only 2 cases of acute otitis media, treated by myringotomy and antibiotics, in which complications developed. One of these patients suffered from a grave systemic disease (plasmocytoma) which probably lowered his resistance against the causing micro-organism. This patient died about a year later from plasmocytoma. Out of 43 cases of acute otitis media with complications, 23 had received no treatment at all prior to admission whereas [illegible] cases had been treated more or less adequately with antibiotics and ear drops prior to the development of complications. One patient had sustained a fracture of the base of the skull, causing a dead ear 8 months prior to admission. This patient, when contracting an acute otitis media in his dead ear developed a fulminant labyrinthogenic meningitis. The value of mastoidectomy has been questioned by McKenzie (1958) Although it is sometimes possible to cure an acute mastoiditis with antibiotic treatment only there is always the risk of the development of fibrosing mastoiditis and adhesive otitis (Palva & Siirala, 1954).

All of our 43 cases of mastoiditis with or without further complications have been treated surgically A subperiosteal abscess was present in 12 cases and an unsuspected epidural or perisinuous abscess was disclosed in 3 cases. Especially in cases with epidural abscess an attempt to cure the disease by conservative means would probably have resulted in even more dangerous complications.

Meningitis is the most frequent intracranial

Table V *CSF findings in intracranial complications of acute and chronic otitis media*

	Proteins (mg %)	Sugar (mg %)	Leucocytes	Bacteria	Remarks
Acute otitis media					
1	33	32	62	—	Sinus thrombosis
2	150	66	2 800	—	Mastoiditis
3	227	13	22 000	Klebsiella	Mastoiditis
4	214	11	70 000	Pneumococci	Acute o. m. Purulent labyrinthitis
5	920	3	11 200	Pneumococci	Mastoiditis
6	120	28	8 300	Pneumococci	Mastoiditis
7	198	47	9 000	Pneumococci	Mastoiditis
8	258	49	6 400	Pneumococci	Mastoiditis
9	400	0	2 900	Pneumococci	Mastoiditis
10	290	11	20 000	Pneumococci	Mastoiditis
Chronic otitis media					
1	152	58	1 100	—	Temporal lobe abscess
2	155	75	4 450	—	Temporal lobe abscess
3	103	61	296	—	Purulent labyrinthitis
4	70	77	85	—	Purulent labyrinthitis
5	117	39	184	—	Purulent labyrinthitis
6	105	69	3 520	Gr. diploc.	Purulent labyrinthitis
7	227	30	1 800	—	Purulent labyrinthitis
8	159	83	856	—	Sinus thrombosis
9	?	?	4 500	—	Sinus thrombosis

Table VI *Age distribution of 96 cases with complications of acute or chronic otitis media*

Age groups (years)	0-	3-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79
Acute o. m.	2	11	16	1	4	3	3	2	1
Chronic o. m.	—	4	6	6	7	10	8	7	5

complication of acute and chronic otitis media in the antibiotic era (Krajina 1956 Proctor 1966) According to many reports, the mortality is still considerable thus Kessler et al. (1970) reported a mortality rate of 33% in their series of 51 cases. It has been stated that meningitis caused by acute otitis media can be managed with antibiotics only (Waring & Smith 1944 Alexander et al. 1953 McLay 1954) On the other hand, dearly bought experience has shown that combined surgical and antibiotic treatment is a safer procedure. This holds true especially for the dreaded otogenic pneumococcic meningitis. Bastrup-Madsen & Norby (1955) lost one third of their patients treated with antibiotics only whereas all those 10 cases where mastoidectomy was carried out recovered Our experience with pneumococcic meningitis has also shown that it is safer to carry out a mastoidectomy as soon as possible in those cases. Bauer (1963) holds the same view All cases of meningitis should be submitted to a careful otorhinological examination in order to disclose the etiology of the meningitis. We have seen several cases of otogenic meningitis having been treated elsewhere with antibiotics for sometimes an unduly long time without result. Not until the condition of the patients had seriously worsened were they sent to the ENT Department.

Lateral sinus thrombosis is nowadays a relatively infrequent complication of otitis media, especially of acute otitis media. According to large statistics, the mortality rate is between 10 and 40% in the antibiotic era (Moser & Ocken 1966) The clinical picture may be completely altered by antibiotic treatment, making the diagnosis sometimes very difficult. The well-known classical signs, spiking fever and signs of septicemia are frequently absent. In all cases of suspected intracranial complication it is extremely important to carry out a spinal puncture and the Tobey–Ayer test should be done at the same occasion The test however is not always conclusive. In our 5 cases of lateral sinus thrombosis the test was negative or uncertain in 3 In the antibiotic era ligation of the internal jugular vein is seldom necessary (Harpman, 1948 Cawthorne 1955) All of our cases were managed without ligature of the vein.

Brain abscess, most frequently caused by chronic otitis media had a very grave prognosis before the advent of antibiotics, the mortality rate being 50–100% In the antibiotic era the prognosis has considerably improved, according to large statistics the mortality rate is nowadays about 25% (Tarkkanen, 1963) The diagnosis may still be difficult in many cases even with the whole modern diagnostic battery (angiography pneumo-encephalography electro-encephalography and isotope scanning) at hand. The clinical picture may be considerably altered by the effect of antibiotic treatment and focal signs are less evident (Krajina 1956 Proctor 1966). It is extremely important to examine all cases with suspected or manifest intracranial complications neurologically prior to instituting any treatment As for the treatment of brain abscess, the modern conception is that the abscess should be evacuated by the neurosurgeon whereas the primary focus in the temporal bone should be treated by the otologist (Cawthorne 1955 Tarkkanen 1963). The outstanding results achieved by neurosurgeons also speak in favour of this view Thus Pennybacker (1961) had a mortality rate of only 5.7% in his series of 35 cases of otogenic brain abscess. As we had no neurosurgeon

t hand, the abscesses were drained through he mastoid cavity in our 2 cases, with good results and without any lasting disability

Chronic otitis media, especially if accom- nied by cholesteatoma still carries the in- erent risk of dangerous complications. Such ases should be rendered safe by elective sur ery before complications have developed, thus is also possible to conserve or even improve he hearing in many cases. In our series holesteatoma was present in 51 out of 53 cases f chronic otitis media with complications. ll cases of chronic otitis media with an exa- erbation and symptoms suggestive of an in- pient complication should be very carefully xamined and surgical treatment should be considered as soon as possible. In our series here are several cases, where an obvious acute exacerbation of a chronic otitis media had been treated with ear drops for more than a week prior to admission. Ear drops and antibiotics are certainly no substitute for adequate sur gery Cases with labyrinthine fistula should, preferably be treated almost as surgical emer gencies. In our series a labyrinthine fistula was present in 42 cases out of 53 and the fistula had caused a suppurative labyrinthitis associated with meningitis in 5 cases. One of our cases with labyrinthine fistula was a very sad one, the patient had one dead ear at the first examination and a labyrinthine fistula in her other useful ear She refused every kind of operation at that time. About half a year later she was brought to the hospital uncon- scious, with a severe labyrinthogenic meningi- tis. She still believes that the operation was the cause of her lost hearing.

ZUSAMMENFASSUNG

96 Falle von Komplikationen akuter und chronischer Mittelohrentzündung werden beschrieben. 43 Kom- plikationen waren von akuter und 53 von chronischer Mittelohrentzündung verursacht. Intrakranielle Kom- plikationen lagen in 29 Fallen vor epiduraler oder perisinöser Abszeß in 8, Sinusthrombose in 5 Me- ningitis in 14 und Schlafenlappenabszeß in 2 Fällen. Alle Falle wurden operativ behandelt, und zwar ohne Mortalität.

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Table VI. *Age distribution of 96 cases with complications of acute or chronic otitis media*

Age groups (years)	0–2	3–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79
Acute o. m.	–	11	16	1	4	3	3	–	1
Chronic o. m.	—	4	6	6	7	10	8	7	5

complication of acute and chronic otitis media in the antibiotic era (Krajina, 1956; Proctor 1966). According to many reports, the mortality is still considerable: thus Kessler et al (1970) reported a mortality rate of 33% in their series of 51 cases. It has been stated that meningitis caused by acute otitis media can be managed with antibiotics only (Waring & Smith, 1944; Alexander et al. 1953; McLay 1954). On the other hand, dearly bought experience has shown that combined surgical and antibiotic treatment is a safer procedure. This holds true especially for the dreaded otogenic pneumococcic meningitis. Bastrup-Madsen & Norby (1955) lost one-third of their patients treated with antibiotics only, whereas all those 10 cases where mastoidectomy was carried out, recovered. Our experience with pneumococcic meningitis has also shown that it is safer to carry out a mastoidectomy as soon as possible in those cases. Bauer (1963) holds the same view. All cases of meningitis should be submitted to a careful otorhinological examination in order to disclose the etiology of the meningitis. We have seen several cases of otogenic meningitis having been treated elsewhere with antibiotics for sometimes an unduly long time, without result. Not until the condition of the patients had seriously worsened were they sent to the ENT Department.

Lateral sinus thrombosis is nowadays a relatively infrequent complication of otitis media, especially of acute otitis media. According to large statistics, the mortality rate is between 10 and 40% in the antibiotic era (Moser & Oeken 1966). The clinical picture may be completely altered by antibiotic treatment making the diagnosis sometimes very difficult. The well known classical signs, spiking fever and signs of septicemia are frequently absent. In all cases of suspected intracranial com[plica]tion it is extremely important to carry o[ut a] spinal puncture and the Tobey-Ayer te[st] should be done at the same occasion. Th[e] test, however, is not always conclusive. In ou[r] 5 cases of lateral sinus thrombosis the test wa[s] negative or uncertain in 3. In the antibiot[ic] era ligation of the internal jugular vein [is] seldom necessary (Harpman, 1948; Cawthorne 1955). All of our cases were managed with[out] ligature of the vein.

Brain abscess, most frequently caused b[y] chronic otitis media, had a very grave progno[sis] before the advent of antibiotics, the mor[tality] rate being 50–100%. In the antibiotic era the prognosis has considerably improved, according to large statistics the mortality ra[te] is nowadays about 25% (Tarkkanen, 1963). The diagnosis may still be difficult in many cases, even with the whole modern diagnostic battery (angiography, pneumo-encephalography, electro-encephalography and isotope scanning) at hand. The clinical picture may be considerably altered by the effect of anti[biotic] treatment and focal signs are less ev[i]dent (Krajina, 1956; Proctor 1966). It is extremely important to examine all cases w[ith] suspected or manifest intracranial complica[tions] neurologically prior to instituting an[tibiotic] treatment. As for the treatment of brain ab[scess], the modern conception is that the ab[scess] should be evacuated by the neurosurgeon whereas the primary focus in the tempora[l] bone should be treated by the otologist (Cawthorne 1955; Tarkkanen, 1963). The [out]standing results achieved by neurosurgeon[s] also speak in favour of this view. Thus Pen[ne]backer (1961) had a mortality rate of on[ly] 5.7% in his series of 35 cases of o[togenic] brain abscess. As we had no neuro[surgeon]

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EXTERNAL EAR PROSTHESES

Medical Film

1971 16 mm colour magnetic sound track 25 minutes

P Vang Jensen

From the Ear Nose and Throat Department and the Department of Photography Rigshospitalet University Hospital Copenhagen Denmark

(Received June 20 197_)

Surgical procedures for reconstruction of major external ear defects are extremely difficult. This film describes a technique by which it is possible to make latex prostheses of the ear with a very close similarity to the natural ear After a short survey the film demonstrates the main points of the technique which are described in detail in *Acta Oto-laryngologica 64* 492–499 (1967).

By showing how good the results can be the film encourages others to take up technique

The film can be borrowed from the Department of Educational Media, Rigshospitalet, Blegdamsvej DK 2100 Copenhagen Ø mark.